Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

Journal Club - Endobronchial Valve Bronchoscopic Lung Volume Reduction

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; Food and Drug Administration, **FDA**; endobronchial valve, **EBV**; forced expiratory volume in 1 second, **FEV_1**; 6-minute walk distance, **6MWD**; standard of care, **SOC**; computed tomography, **CT**; National Emphysema Treatment Trial, **NETT**; lung volume reduction surgery, **LVRS**; minimal clinically important difference, **MCID**

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Keywords

emphysema; chronic obstructive pulmonary disease; COPD; endobronchial valve; lung volume reduction

Introduction

It is estimated that approximately 3.5 million American adults have been diagnosed with emphysema, an irreversible destruction of the alveolar lung parenchyma. In advanced cases, the lung damage is so severe that significant air trapping occurs and does not improve with the use of bronchodilators and other conventional medicines used for chronic obstructive pulmonary disease (COPD). Viable surgical options include bullectomy, lung volume reduction surgery (LVRS), and lung transplantation but many patients may not be appropriate candidates for these procedures and/or there are long wait times for transplantation. Recently, the U.S. Food and Drug Administration (FDA) approved the Zephyr® endobronchial valve (EBV) (Zephyr Valve EBV; Pulmonx Corporation, Redwood City, California) for bronchoscopic lung volume reduction for patients with severe emphysema who are not responsive to medical therapy. This 1-way valve, the size of a pencil eraser, is inserted into the targeted diseased portion of the lung. Typically, 4 to 8 valves are inserted into the chosen emphysematous lobe and will allow air to escape out of that region but prevent any further air from entering, leading to deflation, and ultimately, total lobar collapse over a matter of weeks. An earlier study with the Zephyr® valves, the "Endobronchial Valve for Emphysema Palliation Trial, (VENT)" study,[1] was a multicenter trial with 321 participants (220 with EBV insertion) that demonstrated statistically significant improvements in forced expiratory volume in 1 second (FEV_1) and the 6-minute walk distance test (6MWD) between EBV and standard of care (SoC) groups but these were not clinically meaningful differences (mean change in FEV_1 was 60 mL and median difference from baseline 6MWD 19.1 m).[1] Post hoc analysis indicated that the best responders were those who demonstrated the following criteria: little to virtually no collateral ventilation to ipsilateral adjacent lobes, complete lobar occlusion achieved with the correct occlusive positioning of the valves in all segmental and subsegmental airways and complete intact fissures between lobes.[2,3] With this information, Pulmonx developed a unique technology— Chartis (Pulmonx Corporation, Redwood City, California) a device that tests for collateral ventilation to judge the appropriateness of valve insertion.[4] The Chartis system consists of a console connected to a balloon catheter with a central channel that is used to occlude the target lobe and to subsequently measure pressure and flow to calculate resistance to airflow and hence to quantify collateral ventilation in that lobe.[4] More recently, advanced computed tomography (CT) scan analysis techniques have been developed that can virtually eliminate the need for testing with the Chartis system.[5,6] Advanced CT analysis techniques have become a key element of

deciding on the appropriateness of candidates. This has been confirmed with several short-term single center studies.[2,7,8]

The FDA actually granted the Zephyr® valve "breakthrough device" designation, allowing the FDA to provide guidance on efficient device development and to expedite evidence generation and review of the device. This designation generally signals the recognition that there are relatively few viable options for treating the targeted patient population. Indeed, the first study we review by Criner and colleagues, LIBERATE (below) is the first large, prospective, randomized controlled, multicenter study to evaluate the effectiveness, safety and durability of the benefit out to 12 months in patients with severe heterogeneous emphysema and with little to no collateral ventilation in the target lung. In order to expedite approval, the FDA required that, compared to previous studies, the primary endpoints show a greater magnitude of difference between Zephyr valve insertion and SoC versus a sham procedure and then SoC. In this Journal Club we will review this pivotal study that led to the approval of the Zephyr ® valve in the United States and other recent studies that have evaluated the efficacy and safety of this device.

Note: Abstracts are presented in their original, published format and have not been edited to match JCOPDF style.

Abstract 1
Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

Criner GJ, Sue R, Wright S, et al; LIBERATE Study Group. *Am J Respir Crit Care Med.* 2018;198(9):1151-1164. doi: https://doi.org/10.1164/rccm.201803-0590OC

RATIONALE:
This is the first multicenter randomized controlled trial to evaluate the effectiveness and safety of Zephyr EndobronchialValve (EBV) in patients with little to no collateral ventilation out to 12 months.

OBJECTIVES:
To evaluate the effectiveness and safety of Zephyr EBV in heterogeneous emphysema with little to no collateral ventilation in the treated lobe.

METHODS:
Subjects were enrolled with a 2:1 randomization (EBV/standard of care [SoC]) at 24 sites. Primary outcome at 12 months was the ΔEBV-SoC of subjects with a post-bronchodilator FEV_1 improvement from baseline of greater than or equal to 15%. Secondary endpoints included absolute changes in post-bronchodilator FEV1, 6-minute-walk distance, and St. George's Respiratory Questionnaire scores.

MEASUREMENTS AND MAIN RESULTS:
A total of 190 subjects (128 EBV and 62 SoC) were randomized. At 12 months, 47.7% EBV and 16.8% SoC subjects had a ΔFEV1 greater than or equal to 15% ($P < 0.001$). ΔEBV-SoC at 12 months was statistically and clinically significant: for FEV1, 0.106 L ($P < 0.001$); 6-minute-walk distance, +39.31 m ($P = 0.002$); and St. George's Respiratory Questionnaire, -7.05 points ($P = 0.004$). Significant ΔEBV-SoC were also observed in hyperinflation (residual volume, -522 ml; $P < 0.001$), modified Medical Research Council Dyspnea Scale (-0.8 points; $P < 0.001$), and the BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index (-1.2 points). Pneumothorax was the most common serious adverse event in the treatment period (procedure to 45 d), in 34/128 (26.6%) of EBV subjects. Four deaths occurred in the EBV group during this phase, and one each in the EBV and SoC groups between 46 days and 12 months.

CONCLUSIONS:
Zephyr EBV provides clinically meaningful benefits in lung function, exercise tolerance, dyspnea, and quality of life out to at least 12 months, with an acceptable safety profile in patients with little or no collateral ventilation in the target lobe. Clinical trial registered with www.clinicaltrials.gov (NCT 01796392).

KEYWORDS:
chronic obstructive pulmonary disease; emphysema; lung reduction
PMID: 29787288

Comments

The results of the LIBERATE trial provided the data

that lead to the FDA's approval of the Zephyr® valve. The critical element of the LIBERATE trial was that it followed patients for efficacy, in addition to safety, for 12 months rather than 6 months (see TRANSFORM STUDY published in 2017 below). As mentioned in the introduction, this trial utilized important information from the post hoc analysis of the VENT trial[3,4] and other trials that showed only patients with complete fissures in the treated lung, no evidence of collateral ventilation and in whom lobar occlusion was confirmed, demonstrated statistically significant and clinically meaningful outcomes including for patients with homogenous emphysema. While it was a multicenter study, 18 of the sites were in the United States, 5 in Europe and 1 in Brazil.

Participants had to be between 40 and 75 years of age with a post bronchodilator FEV_1 between 15% and 45% predicted. The total lung capacity had to be greater than 100% of predicted and the residual volume had to be greater than or equal to 175% of predicted. The 6MWD had to be between 100 and 500 meters after a supervised pulmonary rehabilitation program. Only patients who demonstrated no collateral ventilation between target and ipsilateral lobes with post-procedure confirmation of lobar occlusion were included in the trial. The Chartis pulmonary assessment system (Pulmonx, Redwood City, California) was used to assess for collateral ventilation. The selected target lobe had to have greater than 50% destruction (percentage of Voxels less than -910 Hounsfield units on CT) and heterogeneous emphysema, defined as an absolute difference of 15% or greater in destruction scores between the targeted and ipsilateral adjacent lobes.

This study also required greater magnitude of improvement to identify a positive responder including for the improvement in FEV_1 being greater than 15% versus a greater than 12% improvement in the TRANSFORM study (below). Further, the absolute difference of 0.106 L signifies a meaningful important clinical change. The prolonged 12-month follow-up for efficacy and safety, in addition to the higher bar set for the responder rates, are likely the elements that the FDA required as important in granting it the exemption status for expedited approval.

While pneumothorax was the most serious adverse event noted, interestingly those participants who experienced a pneumothorax attained the same level of benefit over the long-term as those without a pneumothorax. The authors also note that the 3 pneumothorax-related deaths occurred in participants who were not treated in the most diseased lobe because of not meeting the heterogeneity requirement and/or the absence of collateral ventilation. This may suggest that participants with reduced capacity in the contralateral lung experience higher risk from the insult of single-lung ventilation during the pneumothorax event. The authors emphasize that physicians performing EBV treatment need to be trained on appropriate patient and lobe selection for treatment and anticipate and recognize a pneumothorax early so it can be readily managed using standard approaches. The investigators in this study admitted patients post procedure for 5 days and ordered daily chest radiographs to assess evidence for a pneumothorax. The first one was taken within the first hour after the procedure.

The benefit seen with regard to 6MWD of 39 meters seen after 12 months was more related to the 26.3 meters decline for the SoC group rather than the absolute improvement of 13 meters in the EBV group. This emphasizes that this procedure may be beneficial not only in terms of the improvements seen as a result of having EBV insertion but also from preventing the decline that may occur in the absence of it.

Further, in contrast to the National Emphysema Treatment Trial (NETT)[9,10] there was no correlation between baseline 6MWD and the changes in primary and secondary outcomes of FEV_1, 6MWD or St George's Respiratory Questionnaire (SGRQ). In other words, in contrast to the NETT trial, where substantial benefit was seen only in patients with low exercise tolerance assessed by baseline 6MWD, this does not appear to influence outcomes with EBV placement.

It is also worth noting that while the study was not powered to demonstrate differences in the rate of respiratory failure events it did indeed demonstrate such with a significant reduction in events in the EBV group versus the SoC group (P=0.033) and showed a trend in reduction of COPD exacerbations resulting in hospitalizations (P=0.053).

The results of the LIBERATE trial are very promising. They demonstrate that responders had improvements comparable to the NETT study and had a 20% wider range of lung function and wider range of exercise tolerance compared to the NETT trial responders. The improvements seen in the LIBERATE trial compared to lung volume reduction surgery include FEV_1

changes of 17% in the EBV group compared to 19% in the LVRS group, 39.3 meters versus 44.7 meters for 6MWD and SGRQ scores of -7.05 versus -13.9 points respectively. There was also improvement in morbidity: pneumothoraxes requiring chest tubes was less than 30% in the EBV group versus greater than 90% in the LVRS group, respiratory failure less than 30% in the EBV group versus greater than 90% in the LVRS group and pneumonia 4% versus 18% respectively.[10]

The authors also concluded that the study might have prevented many participants from potentially benefiting from a revision procedure due to the study design that restricted repeat bronchoscopy for valve revision or replacement only for participants with a total lung volume reduction of less than 50% and incomplete lobar occlusion based on the 45-day CT assessment. In conclusion, this multicenter, prospective randomized controlled trial of the Zephyr® EBV in patients with heterogeneous emphysema without collateral ventilation demonstrated significant and clinically meaningful benefits over current standard of care medical therapy. The benefits were noted in terms of lung function, dyspnea, exercise capacity and quality of life out to at least 12 months following the procedure. Previous studies have suggested these benefits may also be seen in patients with homogenous emphysema.[8,11] The results are comparable to LVRS with less morbidity. Endobronchial valves now provide a viable treatment option for patients with severe emphysema who are not candidates for LVRS or lung transplantation. It is important to consider the observed benefit to risk ratio of EBV treatment in the context of the limited treatment options for patients with severe emphysema. Furthermore, the EBVs are removable if complications arise or if the patient does not respond. While pneumothorax was not uncommon, the rate is similar to that seen in previous studies and the occurrence of pneumothorax does not appear to negatively impact the clinical outcomes as assessed in this study.

Abstract 2
A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM)

Kemp SV, Slebos DJ, Kirk A, et al; TRANSFORM Study Team. *Am J Respir Crit Care Med.* 2017;196(12):1535-1543.
doi: https://doi.org/10.1164/rccm.201707-1327OC

RATIONALE:
Single-center randomized controlled trials of the Zephyr endobronchial valve (EBV) treatment have demonstrated benefit in severe heterogeneous emphysema. This is the first multicenter study evaluating this treatment approach.

OBJECTIVES:
To evaluate the efficacy and safety of Zephyr EBVs in patients with heterogeneous emphysema and absence of collateral ventilation.

METHODS:
This was a prospective, multicenter 2:1 randomized controlled trial of EBVs plus standard of care or standard of care alone (SoC). Primary outcome at 3 months post-procedure was the percentage of subjects with FEV_1 improvement from baseline of 12% or greater. Changes in FEV_1, residual volume, 6-minute-walk distance, St. George's Respiratory Questionnaire score, and modified Medical Research Council score were assessed at 3 and 6 months, and target lobe volume reduction on chest computed tomography at 3 months.

MEASUREMENTS AND MAIN RESULTS:
Ninety-seven subjects were randomized to EBV (n = 65) or SoC (n = 32). At 3 months, 55.4% of EBV and 6.5% of SoC subjects had an FEV_1 improvement of 12% or more ($P < 0.001$). Improvements were maintained at 6 months: EBV 56.3% versus SoC 3.2% ($P < 0.001$), with a mean ± SD change in FEV_1 at 6 months of 20.7 ± 29.6% and -8.6 ± 13.0%, respectively. A total of 89.8% of EBV subjects had target lobe volume reduction greater than or equal

to 350 ml, mean 1.09 ± 0.62 L (P < 0.001). Between-group differences for changes at 6 months were statistically and clinically significant: ΔEBV-SoC for residual volume, -700 ml; 6-minute-walk distance, +78.7 m; St. George's Respiratory Questionnaire score, -6.5 points; modified Medical Research Council dyspnea score, -0.6 points; and BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, -1.8 points (all P < 0.05). Pneumothorax was the most common adverse event, occurring in 19 of 65 (29.2%) of EBV subjects.

CONCLUSIONS:
EBV treatment in hyperinflated patients with heterogeneous emphysema without collateral ventilation resulted in clinically meaningful benefits in lung function, dyspnea, exercise tolerance, and quality of life, with an acceptable safety profile. Clinical trial registered with www.clinicaltrials.gov (NCT02022683).

KEYWORDS:
chronic obstructive pulmonary disease; collateral ventilation; endobronchial valves; hyperinflation; lung volume reduction
PMID:28885054

Comments

The TRANSFORM trial was a smaller multicenter, randomized controlled trial, (only 97 patients), at 17 sites across Europe and only lasted 6 months. Patients in the TRANSFORM study had entry criteria similar to the LIBERATE study except residual volume had to be greater than or equal to 180% predicted, (compared to 175% predicted in the LIBERATE study). In TRANSFORM, heterogeneous emphysema was defined as a greater than 10% difference in destruction scores between target and ipsilateral lobes, (compared to 15% in LIBERATE). The study also utilized the CHARTIS system to assess the presence of collateral ventilation between target and adjacent lobes. This study also did not have a sham bronchoscopy in the SoC group. The authors argued however that the benefit of EBV treatment using a sham control had already previously been demonstrated.[12] Patients did undergo bronchoscopy for the purposes of CHARTIS examination but patients who demonstrated collateral ventilation had their procedure terminated at that point (similar to TRANSFORM). The authors acknowledge that this does not entirely mitigate against any placebo effect associated with actual valve implantation. Patients also were not required to have mandatory pulmonary rehabilitation in the period before trial entry but given that randomization occurred this should be balanced across the 2 groups. Slight imbalances were noted in the absolute FEV_1 and, to a lesser extent, SGRQ at baseline between the EBV group and the SoC group. However, analysis of covariance models suggested that the group differences are valid despite the groups having different baseline values

In contrast to the LIBERATE study, patients were considered to be responders if they had at least a 12% improvement from baseline in FEV_1. This study did demonstrate improvements that exceeded the minimal clinically important difference (MCID) for FEV_1, SGRQ, residual volume, 6MWD and modified Medical Research Council scores at 6 months post treatment. Patients in this study will be followed for a total of 24 months. Post hoc analysis of the study once again demonstrated the critical importance of the absence of collateral ventilation and achieving complete lobar occlusion. This study also demonstrated the suitability for both upper and lower lobe disease.

Abstract 3
Complications Related to Endoscopic Lung Volume Reduction for Emphysema with Endobronchial Valves: Results of a Multicenter Study

Fiorelli A, D'Andrilli A, Bezzi M, et al. *J Thorac Dis*. 2018;10 (Suppl. 27):S3315-S3325.
doi: https://doi.org/10.21037/jtd.2018.06.69

BACKGROUND:
Despite bronchoscopic lung volume reduction (BLVR) with valves is a minimally invasive treatment for emphysema, it can associate with some complications. We aimed at evaluating the rate and type of complications related to valve treatment and their impact on clinical outcomes.

METHODS:
It is a retrospective multicenter study including all consecutive patients with severe heterogeneous

emphysema undergoing BLVR with endobronchial valve treatment and developed any complications related to this procedure. The type of complication, the time of onset, the treatment required and the out-come were evaluated. Response to treatment was assessed according to the minimal clinically important difference (MCID) as follows: an improvement of ≥15% in forced expiratory volume in one second (FEV1); of -8% in residual volume (RV); of ≥26 m in 6-minnute walking distance (6MWD); and of ≥4 points on the St. George's Respiratory Questionnaire (SGRQ). Target lobe volume reduction (TLVR) ≥350 mL was considered significant.

RESULTS:
One hundred and seven out of 423 (25.3%) treated patients had complications related to valve treatment including pneumothorax (17.3%); pneumonia (1.7%), chronic obstructive pulmonary disease (COPD) exacerbation (0.9%), respiratory failure (1.4%), valve migration (2.1%), and hemoptysis (1.9%). In all cases complications resolved with appropriate treatment including removal of valves in 21/107 cases (19.6%). Patients with TLVR ≥350 mL (n=64) vs. those <350 mL (n=43) had a statistically significant higher improvement in FEV1 (19.0%±3.9% vs. 3.0%±0.9%; P=0.0003); in RV (-10.0%±4.8% vs. -4.0%±2.9%; P=0.002); in 6MWD (33.0±19.0 vs. 12.0±6.3 metres; P=0.001); and in SGRQ (-15.0±2.9 vs. -8.0±3.5 points; P=0.01). Only patients with TLVR ≥350 mL met or exceeded the MCID cut-off criteria for FEV1 (19.0%±3.9%), RV (-10.0%±4.8%), 6MWT (33.0±19.0 metres), and SGQR (-15.0±2.9 points). Five patients (1.2%) died during follow-up for causes not related to valves treatment neither to any of the complications described.

CONCLUSIONS:
Valve treatment is a safe and reversible procedure. The presence of complications seems not to have a significant impact on clinical outcome in patients with lobar atelectasis. Due to poor clinical conditions and possible complications, BLVR should be performed in high volume centers with a multidisciplinary approach.

KEYWORDS:
Zephyr endo-bronchial valves; bronchoscopic lung volume reduction (BLVR); emphysema.

Comments

This is a retrospective study of several Italian centers that performed Zephyr® EBV between 2012 and 2017. It reviews all patients consecutively treated in that time period. Their safety findings are consistent with the results reported in previous single center and multicenter prospective trials.

Abstract 4
Lung Volume Reduction with Endobronchial Coils for Patients with Emphysema

Welling JBA, Slebos DJ. *J Thorac Dis.* 2018;10(Suppl 23):S2797-S2805.
doi: https://doi.org/10.21037/jtd.2017.12.95

The lung volume reduction coil treatment is a minimally invasive bronchoscopic treatment option for emphysema patients who suffer from severe hyperinflation. The treatment is aimed at a large group of patients where lung volume reduction surgery and bronchoscopic lung volume reduction using endobronchial valves are no option, or alternatively, can be offered as a bridge to lung transplantation. The nitinol coil exhibits a shape memory effect and is biologically inert. The lung volume reduction coil procedure is performed in two separate treatment sessions, targeting one lobe per session, with the contralateral lobe being treated 4 to 8 weeks after the first session. In one treatment session, around 10 to 14 coils, thereby treating an entire lobe, are being placed. Selecting optimally treated, symptomatic chronic obstructive pulmonary disease (COPD) patients with emphysema and severe hyperinflation, while avoiding significant airway disease such as asthma, chronic bronchitis and bronchiectasis, is key to achieve treatment success. Three randomized clinical trials investigating lung volume reduction coil treatment have been published until now, reporting the results of 452 treated patients up to 12 months after coil treatment. Lung volume reduction coil treatment results in significant improvement of pulmonary function outcomes and quality of life in patients with severe hyperinflation. The most common complications of lung volume reduction coil treatment

are: COPD exacerbations, pneumonia, Coil Associated Opacity and an increased risk of pneumothorax. The purpose of this article is to describe the coil technique and review the available literature regarding effect, safety and future perspectives of lung volume reduction with coils for emphysema patients.

KEYWORDS:
Lung volume reduction; bronchoscopy; chronic obstructive pulmonary disease (COPD); coils; emphysema

Comments

These coils are shape-memory nitinol devices implanted with a bronchoscope under fluoroscopic guidance. They are straightened for deployment and gather up loose lung parenchyma as they revert to their original double-loop shape within the airway. Multiple coils implanted throughout a lobe achieve mechanical volume reduction through distribution of increased radial tension throughout the airway network, while tethering open small airways to prevent collapse. This review of these studies suggests these may be a viable option for individuals who may not be candidates for the endobronchial valves.

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