TRANSFORM - THE FIRST MULTICENTER RANDOMIZED TRIAL OF ZEPHYR ENDOBRONCHIAL VALVE TREATMENT IN HETEROGENEOUS EMPHYSEMA

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THE CLINICAL QUESTION

Can Zephyr endobronchial valves (EBVs) be safely and effectively used in patients with heterogeneous emphysema and absent collateral ventilation (CV) as compared to standard of care (SoC)?

TAKE HOME MESSAGE

Bronchoscopic lung volume reduction (BLVR) using EBV in hyperinflated patients with heterogeneous emphysema and absent CV in the target lobe results in clinically significant improvement in lung function, dyspnea, exercise tolerance and quality of life over standard medical management. These benefits are consistent with prior trials results and in line with those seen with lung volume reduction surgery (LVRS). BLVR is a reversible procedure with potential lower morbidity than LVRS making it a good option for symptomatic patients despite maximal medical treatment. Pneumothorax is a serious and potentially fatal side effect that requires an established management protocol in place before performing the procedure.

BACKGROUND

LVRS has shown improvements in FEV1, walking distance, quality of life, and survival in selected patients with heterogeneous emphysema. Despite the proven benefits, LVRS is not widely adopted, being an invasive procedure and related morbidity and mortality. BLVR with Zephyr EBVs (one-way valves) aims to achieve the benefits seen with LVRS with less morbidity.
The VENT study was a multicenter trial that demonstrated statistical but not clinically meaningful improvement in FEV1 and six-minute walk distance (6MWD) between the EBV and SoC groups. Post hoc analysis showed the clinically meaningful outcomes in patients with little or no CV between the target and ipsilateral lobes when complete lobar occlusion was achieved, highlighting the importance of the absence of CV.
Selection criteria of subsequent studies focused on emphysema patients with targets that had no interlobar CV and found clinically and statistically meaningful benefits in multiple outcome measures. This has been demonstrated in patients with heterogeneous (BeLieVer-HIFI and STELVIO) and homogenous emphysema (IMPACT and STELVIO).
BeLieVer-HIFI and STELVIO were single-center RCTs that have shown the benefit of BLVR using the Zephyr EBV when compared to standard medical therapy. TRANSFORM is the first multicenter study in patients with heterogeneous emphysema and absent CV.

STUDY DESIGN

Type of trial: prospective, randomized, controlled, two-armed multicenter trial without blinding or sham procedure
N: 97, randomized 2:1
EBV: 65
SoC: 32
Study groups: ex-smokers, greater than 40 years old with severe emphysema
Settings: 17 European sites
Enrollment: June 2014 to June 2016
Treatment period/Follow up: 6 months

Primary outcome
Percentage of patients in the EBV group at three months with ≥12% improvement in FEV1 (Minimal clinical importance difference [MICD]) compared with the SoC group.

Secondary outcomes
A comparison between EBV and SoC groups for the absolute and percent changes as well as for responders rates (the percentage of patients achieving the MCID) at 3 and six months for:
FEV1, RV, SGRQ, 6MWD, mMRC scores.

For the EBV group only:
the absolute and percentage change in TLVR at 45 days
the percentage of patients meeting the TLVR MCID of ≥ 350 ml

Intervention
Before randomization, all candidates underwent an evaluation to exclude presence of interlobar CV using Chartis (An endoscopic, balloon catheter system that quantifies CV by detecting real-time flow and pressure for specific lobes). Patients with CV-negative target lobe were randomized in a 2:1 manner into either the EBV group or the SoC alone group.
Patients randomized to the EBV group underwent placement of Zephyr EBVs immediately following the Chartis assessment to achieve complete lobar occlusion. Target lobe selection with the highest destruction score (on HRCT) was selected first. If CV-positive, the next potential target lobe was evaluated. Patients in this group stayed at least one additional day in the hospital whereas patients in the SoC group were discharged same day per post bronchoscopy discharge protocol.

POPULATION

Inclusion criteria
- Patients ≥ 40 years with heterogeneous emphysema
- A heterogeneity index of ≥10 % between target and adjacent lobes
- CV negative target lobe
- Non-smoker >8 weeks
- FEV1 ≥ 15% predicted and ≤ 45% predicted
- total lung capacity (TLC) > 100% predicted,
- Residual volume (RV) ≥ 180% predicted
- 6MWD ≥150m and ≤450 m

Exclusion criteria
- Active pulmonary infection
- 2 or more exacerbations requiring hospitalization over the past 12 months.
- Greater than two tablespoons of sputum production per day
- Hypercapnia ($PaCO_2$ >7.33)
- Daily use of > 25mg Prednisolone (or equivalent)
- Current diagnosis of asthma
- Significant bronchiectasis on CT scan
- Pulmonary nodule requiring further workup
- Prior LVR or LVRS procedure
- Evidence of pleural adhesions or earlier pulmonary surgery
- Severe Bullous Emphysema (> 1/3 Hemithorax)
- Pulmonary hypertension
- Myocardial infarction or significant cardiovascular events in the past 6 months
- Pregnant or nursing women

Baseline Characteristics
Baseline characteristics were similar in both groups except for:
- Absolute FEV1 0.78±0.24 L in EBV vs. 0.94±0.31 L in Soc (p= 0.008)
- SGRQ score 64.3±14.4 in EBV vs. 58.1±13.3 in SoC (p=0.042)

There was no significant difference in the following parameters:
- GOLD stage III 40% in EBV vs. 56% in SoC
- GOLD stage IV 60% in EBV vs. 44% in SoC
- FEV1, % predicted 29.8±9.2 in EBV vs. 32.2+8.4 in SoC
- RV 249.4±51.8 in EBV vs. 241.0±41.4 in SoC
- TLC 139.0±18.9 vs. 137.3±12.5
- Heterogeneity index between target and ipsilateral lobes 21.8±14.6 in EBV vs 25.5±15.8 in soC

OUTCOMES

Primary outcomes:
At three months, responder rates (FEV1 improved by ≥12% from baseline) were 55.4% in the EBV group and 6.5% in the SoC group (P<0.001). Improvements were maintained at 6 months: EBV 56.3% vs. SoC 3.2% (P<0.001).

Secondary outcomes:
Statistically and a clinically significant improvement from baseline was seen at 3 and six months in the EBV group compared with the SoC group.

Mean changes from baseline in the ITT population at 6 Months:
- FEV1, L 0.14±0.24 vs -0.09±0.14 (P<0.001)
- FEV1% 20.7±29.6 vs -8.6±13.0 (P<0.001)
- RV -0.66±1.04 vs. 0.01±0.79 (P<0.001)
- 6MWD 36.2±76.9 vs. -42.5±68.2 (P<0.001)
- SGRQ -7.2±15.1 vs -0.7±10.4 (P=0.031)
- mMMRC -0.56±1.04 vs. 0.00±0.86 (P=0.010)
- BODE -0.97±2.01 vs. 0.79±1.17 (P<0.001)

MCID responders for key outcome measures in the ITT population at 6 months:
- FEV1 (MCID≥+12%) EBV 56.3% vs. SoC 3.2% (P<0.001)
- RV (MCID≤-430 ml) EBV 57.8% vs. SoC 25.8% (P=0.003)
- SGRQ (MCID≤-4 points) EBV61.7% vs. SoC 34.4% (P=0.042)
- 6MWD (MCID≥+26 m) EBV 52.4% vs. 12.9% (P<0.001)
- mMRC (MCID≤-1 point) EBV 43.8% vs. SoC 22.6% (P=0.032)

At 45 days, 89.8% of patients in the EBV group achieved the MCID for TLVR (≥350 ml)

Adverse events:
Respiratory-related serious adverse events (SAE) were significantly higher in the EBV group.
At six months, there were 44 respiratory related SEAEs in 31 (47.7%) patients in the EBV group vs. four events in 3 (9.4%) patients in the SoC group.

Respiratory-related SAEs in the EBV group at 30 days:
- Pneumothorax 29.2% (20 in 19/65 patients)
- Dyspnea 7.7%
- COPD exacerbation 4.6%
- Pneumonia 4.6%

Pneumothorax
- 20 pneumothoraces in 19/65 patients
- The median time to occurrence of 1 day
- 11 patients required chest tube placement
- One patient required surgical treatment of air leak
- Five patients required valve removal
- One patient died due to cardiac arrest following pneumothorax

COMMENTARY

This is the first multicenter, prospective RCT of Zephyr EBV treatment in patients with severe heterogeneous emphysema and absence of CV. 90% of patients in the EBV group achieved TLVR and experienced improvements that surpassed the MCIDs for FEV1, RV, 6MWD, SGRC, and mMRC at 6 months follow up. This study adds significantly to the evidence that BLVR is an effective treatment for patients with absent CV. The author advocates for the Chartis system as a more reliable tool than visual fissure analysis for assessment of CV. This study demonstrated that BLVR is appropriate for both upper and lower lobe disease, and is a reversible procedure.

The TRANSFORM study was a smaller multicenter RCT with 97 patients that were only followed for six months. Patients will further be followed for a total of 24 months. The study did not have a sham bronchoscopy in the SoC group and led to potential bias in reporting symptoms. Undergoing pulmonary rehabilitation was not mandatory before enrollment, which is the standard of care for patients with severe COPD. Slight differences were noted in the absolute FEV1 and SGRQ at baseline between the EBV group and SoC group. Given the randomization, these differences were balanced across the two groups, and analysis of covariance models suggested that the group differences are valid. Pneumothorax is a serious side effect of this procedure with a rate of 29%, that is higher than prior Zephyr EBV treatment studies (BeLieVeR-HIFi 8%, STELVIO 18% and IMPACT 26%). Mean time to the occurrence was one-day post-procedure, and one patient died while there was an established protocol in place for immediate management. Further discussion regarding safer post procedure protocols is needed. While pneumothorax was the most serious adverse event noted, patients who experienced pneumothorax and survived, did achieve the same level of benefit throughout the study as those without a pneumothorax.

FUNDING

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SUGGESTED READING

1. Washko GR, Fan VS, Ramsey SD, Mohsenifar Z, Martinez F, Make BJ, Sciurba FC, Criner GJ, Minai O, DeCamp MM, Reilly JJ. The effect of lung volume reduction surgery on chronic obstructive pulmonary disease exacerbations. American Journal of Respiratory and Critical Care Medicine. 2008 Jan 15;177(2):164-9.
2. DeCamp Jr MM, Lipson D, Krasna M, Minai OA, McKenna Jr RJ, Thomashow BM. The evaluation and preparation of the patient for lung volume reduction surgery. Proceedings of the American Thoracic Society. 2008 May 1;5(4):427-31.
3. Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, Kovitz KL, Chiacchierini RP, Goldin J, McLennan G. A randomized study of endobronchial valves for advanced emphysema. New England Journal of Medicine. 2010 Sep 23;363(13):1233-44.
4. Valipour A, Slebos DJ, Herth F, Darwiche K, Wagner M, Ficker JH, Petermann C, Hubner RH, Stanzel F, Eberhardt R. Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT study. American journal of respiratory and critical care medicine. 2016 Nov 1;194(9):1073-82..
5. Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD, Hansell DM, Rubens MB, Banya W, Polkey MI, Shah PL. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. The Lancet. 2015 Sep 12;386(9998):1066-73.
6. Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. New England Journal of Medicine. 2015 Dec 10;373(24):2325-35.

ARTICLE CITATION

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