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Short communication

A multicenter, prospective, single-arm clinical investigation of a modified staged treatment algorithm using the AeriSeal system - The STAGE trial

T. David Koster [a,*], Ralf Eberhardt [b], Ralf-Harto Huebner [c], Arschang Valipour [d], Felix Herth [e], Karin Klooster [a], Narinder S. Shargill [f], Sri Radhakrishnan [f], Dirk-Jan Slebos [a]

[a] Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[b] Department of Pneumology and Critical Care Medicine, Asklepios Klinik Barmbek, Hamburg, Germany
[c] Department of Internal Medicine/Infectious Diseases & Respiratory Medicine, Charité, Universitätsmedizin Berlin, Berlin, Germany
[d] Department of Respiratory and Critical Care Medicine, Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria
[e] Department of Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg and Translational Lung Research Center Heidelberg, Heidelberg, Germany
[f] Pulmonx Corporation, Redwood City, CA, USA

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ABSTRACT

Introduction: Treatment with AeriSeal is an alternate treatment option to achieve lung volume reduction in patients with severe COPD and emphysema who are not eligible for valve treatment. This study aimed to assess the safety and mode of action of a modified staged treatment algorithm with a staged treatment with lower dose of AeriSeal.

Methods: We performed a prospective, multicenter feasibility study. AeriSeal was administered during two sequential bronchoscopies: 2 subsegments of a lobe treated with two 5 mL doses, followed by two 10 mL doses in a contralateral lobe after 6 weeks.

Results: A total of 14 patients (36% male, mean FEV_1 28.4% ± 6.7% of predicted) were enrolled. Ten patients completed both treatments, four were treated unilaterally. AeriSeal treatment resulted in significant TLVR (median 220.5 mL) at 3 months follow up. There were no significant changes from baseline at 12 months in lung function, exercise capacity and quality of life. During the 3-month post-treatment period, respiratory SAEs included 5 COPD exacerbations in 4 (28.6%) subjects, post-treatment acute inflammatory response (PAIR) in 2 (14.3%) subjects, and 1 respiratory failure event in 1 (7.1%) subject.

Conclusion: The staged and lower dosed administration of AeriSeal does not impact the overall safety profile in terms of reducing the type and frequency of respiratory SAEs previously reported for a single-stage treatment. A larger volume of AeriSeal than used in this study may be necessary to provide meaningful clinical benefits.

1. Introduction

Bronchoscopic lung volume reduction (BLVR) with endobronchial valves is an established treatment option in patients with severe emphysema and hyperinflation without interlobar collateral ventilation [1–3]. Endobronchial valves are not effective in patients with collateral ventilation and therefore there remains a need for an alternate treatment option for these patients [4].

The AeriSeal System (PulmonX Corp., CA, USA), a cross-linked foam (2.1% aminated polyvinyl alcohol, 1,25% glutaraldehyde, and air) bronchoscopically delivered is a therapeutic device that has the potential for providing multiple severe emphysema treatment approaches. AeriSeal foam has been shown to significantly improve lung function and quality of life in patients with advanced emphysema [5–8]. The foam functions by blocking both small airways and collateral channels causing absorption atelectasis in the treated regions resulting in reduction of hyperinflation [5]. The ASPIRE study, which was discontinued for non-regulatory reasons, showed clinically meaningful and statistically significant improvements in lung function, exercise capacity and quality of life at 6-months post-treatment compared to the standard-of-care control group; however, the overall incidence of adverse events in the AeriSeal treated patients was also prominent [5].

* Corresponding author. Department of Pulmonary Diseases, AA11 University Medical Center Groningen, University of Groningen, PO Box 30.001, 9700 RB, Groningen, the Netherlands.
E-mail address: t.d.koster@umcg.nl (T.D. Koster).

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The crosslinking of AeriSeal foam to surrounding tissue yields a subacute inflammation that is hypothesized to be a function of the volume of AeriSeal delivered [5]. Most patients have historically been treated with a fixed volume of 20 mL foam in each target subsegment (80 mL in total). The current study was designed to evaluate the short-term and long-term safety and mode of action of a modified staged treatment algorithm with an escalation of volume of AeriSeal foam. Specifically, it assessed whether lowering the volume of tissue treated in a single session combined with a staged treatment has an impact on the intensity of the inflammatory response and associated adverse events.

2. Methods

This was a prospective multicenter (4 centers) study (STAGE trial NCT02877459) that included patients with emphysema and hyperinflation (Residual Volume >175% of predicted). The primary treatment targets were regions with the highest emphysema destruction scores and lowest perfusion. Emphysema scores on a segmental level were based on quantitative CT-scan analysis by the StratX® platform (Pulmonx Inc, Redwood City, CA, USA), perfusion was measured with perfusion scintigraphy. Treatment with AeriSeal foam was staged i.e., the desired amount of AeriSeal was delivered over 2 treatment session separated by at least 8 weeks. During the first treatment with AeriSeal, two non-adjacent subsegments in one lobe were treated with 5 mL of AeriSeal each (total volume of 10 mL for the lobe). During the second treatment, approximately 2 months after the first treatment, 2 non-adjacent subsegments in a contralateral lobe were treated with 10 mL of AeriSeal each (total volume of 20 mL for the lobe). An HRCT scan was acquired after three months to determine target lobar volume reduction (TLVR). Lung function, exercise capacity, quality of life, and solicitation of adverse events were evaluated up to 12-months after the second treatment.

3. Results

A total of 14 patients (36% male, mean age 64 ± 6.2 years; mean FEV_1 28.4% ± 6.7% of predicted; RV 237% ± 54% of predicted) were enrolled. Ten completed both treatments, four completed the first treatment. The patients not receiving the second treatment experienced a serious adverse event (SAE) after the first treatment and either did not want to have the second treatment (n = 1) or the Investigator decided not to continue (n = 3).

AeriSeal treatment resulted in significant TLVR at 3 months follow up. The median TLVR was 111 mL (range −39 to −280) (p = 0.005) after the first treatment with AeriSeal with 2 x 5 mL and 117.5 mL (range 1 to −651) (p = 0.002), after the second treatment with 2 × 10 mL (Table 1). For the patients who received both treatments, median TLVR was 220.5 mL (range −38 to −775). There were no significant changes from baseline at 12 months in lung function, exercise capacity and quality of life (Table 2).

During the 3-month post-treatment period, respiratory SAEs included 5 COPD exacerbations in 4 (28.6%) subjects, post-treatment acute inflammatory response (PAIR) in 2 (14.3%) subjects, and 1 respiratory failure event in 1 (7.1%) subject. No patients experienced a pneumothorax. All but one event occurred after the first treatment. Between 3 months and 12 months after the last treatment, there were a total of 5 respiratory SAEs with 3 COPD exacerbations in 3 (21.4%) subjects, formation of a lung cavity in 1 (7.1%) subject and hypercapnia in 1 (7.1%) subject. Three of these events were deemed as "not related" to the device, one COPD exacerbation was "possible", and the lung cavity was "probable" for relatedness to the device. There were no device-related or procedure-related deaths during the course of the study.

Table 1
Baseline characteristics. Values are means ± SD; ‡ St. George's Respiratory Questionnaire (SGRQ) scores range from 0 to 100, with higher scores indicating worse quality of life. § Modified Medical Research Council dyspnea (mMRC) scores scale ranges from 0 to 4, with higher scores indicating more severe dyspnea. Abbreviations: BMI = Body Mass Index; FEV1 = Forced Expiratory Volume in 1 s; RV = Residual volume; FVC = Forced Vital Capacity; DLco = Carbon monoxide diffusing capacity; 6MWD = six-minute walk test; SGRQ = St George's Respiratory Questionnaire; mMRC = Modified Medical Research Council Dyspnea Score.

BASELINE CHARACTERISTICS (n = 14)	
Gender	5 Males (36%) 9 Females (64%)
Age (years)	64.3 ± 6.2
BMI (kg/m^2)	23.7 ± 4.5
Pack Years	37.5 ± 10.4
FEV_1 (%pred)	28.4 ± 6.7
RV (%pred)	237 ± 54
RV/TLC (%)	64.9 ± 7.3
DL_{CO} (% predicted)	31.1 ± 7.0
6MWD (m)	312 ± 54
SGRQ Total score ‡	57.5 ± 13.2
mMRC Dyspnea Score §	2.8 ± 0.6

Table 2
Treatment Results. # Follow-up volume assessments performed 3-months after Treatment #2. Thus, the Treatment #1 follow-up volume is at 5 months post-Treatment #1. Total TLVR reflects a pooling of 5-month for first treated lobe and 3-months for the second treated lobe. Abbreviations: FEV1 = Forced Expiratory Volume in 1 s; RV = Residual volume; 6MWD = Six-minute walk test; SGRQ = St George's Respiratory Questionnaire; mMRC = Modified Medical Research Council Dyspnea Score; TLVR = target lobe volume reduction.

TREATMENT SITES		
Lobes Treated	Treatment #1 (n)	Treatment #2 (n)
Right Upper Lobe (RUL)	7	4
Right Lower Lobe (RLL)	0	1
Left Upper Lobe (LUL)	6	5
Left Lower Lobe (LLL)	1	0
CT RESULTS		
Target Lobe Volume Reduction#	**Median (Min, Max)**	**P-value**
First treatment (mL) (n = 14)	111.0 (−39, 280)	0.005
Second treatment (mL) (n = 10)	117.5 (1, 651)	0.002
Total TLVR (combined) (n = 10)	220.5 (−38, 775)	0.004
EFFICACY		
Change from Baseline to 12 months follow up	**Median (Min, Max) (n = 10)**	**P-value**
Percent FEV_1 (L)	−9.4 (−20.6, 57.0)	0.083
Percent RV (L)	1.77 (−22.0, 30.9)	0.492
6MWD (m)	34 (−50, 136)	0.266
SGRQ (points)	2.4 (−35.3, 12.3)	0.770
mMRC (points)	0 (−2, 1)	0.531

4. Discussion

Our data shows that AeriSeal treatment produces a dose dependent reduction in hyperinflation of the treated areas in the lung with a 10 mL dose causing a lobar volume reduction of approximately 100 mL. Because the administered doses of AeriSeal were rather small compared to the previously used volumes, the overall changes in TLVR were not large enough to have an impact on any clinical outcome measure. Our data suggest that a larger volume of AeriSeal would be required to achieve a meaningful target lobar volume reduction and associated clinical benefit [5].

The frequency of observed SAEs in this study were comparable to what had been previously observed. COPD exacerbations were seen in 15–40% compared to 42% in this present study, pneumonia was

reported between 6 and 24% compared to 0% and PAIR 8.5% compared to 14% [5–8]. Most of the SAEs in this study occurred after the first treatment (2x5mL administration AeriSeal). These data suggest that changing the treatment algorithm to a lower dose or 2 treatment sessions may not change the safety profile from what has been previously reported. The overall incidence of SAEs seen in this study and ASPIRE is not different from the rate of SAEs seen for the endobronchial valves or vapor [5,9].

An alternative treatment approach using AeriSeal is currently being evaluated in patients who are not eligible for valve treatment due to the presence of collateral ventilation with small fissure gaps. A small dose of AeriSeal (up to 40 mL) is administered in subsegments feeding the defined fissure gap to close the airway and block the collateral ventilation to potentially make these patients eligible for valve treatment (NCT04559464).

In conclusion, the staged administration of AeriSeal does not impact the overall safety profile in terms of reducing the type and frequency of respiratory SAEs previously reported for a single-stage treatment. Based on the observed decrease in CT derived hyperinflation, there is a dose-dependent effect of AeriSeal, with a larger volume of AeriSeal than used in this study may be necessary to provide meaningful clinical benefits.

CRediT authorship contribution statement

T. David Koster: Investigation, Writing – original draft, Formal analysis. **Ralf Eberhardt:** Investigation, Writing – review & editing, Data curation. **Ralf-Harto Huebner:** Investigation, Writing – review & editing, Data curation. **Arschang Valipour:** Investigation, Writing – review & editing, Data curation. **Felix Herth:** Investigation, Writing – review & editing, Data curation. **Karin Klooster:** Investigation, Writing – review & editing, Data curation. **Narinder S. Shargill:** Conceptualization, Writing – review & editing, Formal analysis, Methodology, Resources, Data curation. **Sri Radhakrishnan:** Conceptualization, Writing – review & editing, Formal analysis, Methodology, Resources, Data curation. **Dirk-Jan Slebos:** Investigation, Writing – review & editing, Data curation.

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