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EXPERT REVIEWS

Assessment of a novel lung sealant for performing endoscopic volume reduction therapy in patients with advanced emphysema

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AeriSeal® Emphysematous Lung Sealant is a novel endoscopic lung-volume reduction therapy designed to reduce hyperinflation and improve pulmonary function and quality of life in patients with advanced emphysema. The device is administered to the subsegmental bronchus via a catheter as a 20 ml volume of liquid–foam. It flows into the peripheral airways and alveoli where it polymerizes and functions as a tissue glue, forming a film of material on the lung surface that seals the target region to cause durable absorption atelectasis. The AeriSeal System received CE mark approval for the treatment of patients with advanced upper lobe predominant and homogeneous emphysema based upon favorable results from clinical studies, and is commercially available in Europe. Patient and treatment site selection algorithms have been developed to simplify product use and optimize outcomes. This manuscript summarizes how the device is used, its mechanism of action and clinical trial results supporting its safety and efficacy.

Keywords: bronchoscopic lung volume reduction • emphysema therapy • interventional pulmonology • lung volume reduction

The AeriSeal® System is a new-generation endoscopic lung-volume reduction device for treating patients with end-stage pulmonary emphysema, a common, debilitating form of chronic obstructive pulmonary disease (COPD) characterized by inflammatory destruction of lung tissue. Emphysema results from exposure to toxic fumes, most commonly cigarette smoke [1]. The disease is progressive and irreversible, affecting more than 15 million people worldwide, and is a major cause of morbidity and mortality [2]. Emphysema is unique among the different forms of COPD in that it affects the alveolar tissue. By contrast, other forms of COPD, which include chronic asthma, chronic bronchitis, bronchiectasis and bronchiolitis, primarily affect the airways [1]. In emphysema, chronic inflammation, associated with release of proteases and formation of free radicals by macrophages and neutrophils, damages the collagen and elastin fibers of the lung parenchyma, resulting in loss of tissue elasticity [3]. This has two physiological consequences. First, the airways, which are tethered open by the surrounding tissues, collapse prematurely as the lung deflates. Second, as elasticity is lost, the recoil pressure that drives gas out of the lung during exhalation is diminished. Both of these factors contribute to hyperinflation and gas trapping [4,5].

As emphysema progresses, the lungs become too large to fully expand and function effectively within the rigid chest cavity. Exercise capacity is reduced due to ventilatory limitation since the ability to increase minute ventilation by taking deeper breaths is compromised. The respiratory muscles are forced to function at a mechanical disadvantage and work of breathing is increased. Patients experience persistent shortness of breath and poor quality of life. Medical therapy for patients with advanced emphysema consists primarily of bronchodilator therapy and anti-inflammatory drugs, which help open narrowed airways. While these medications are effective for patients with COPD due to

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chronic bronchitis and asthma, they are much less effective for patients with emphysema whose primary abnormality is lung hyperinflation due to destruction of elastic tissue.

Surgical therapies for emphysema, including lung transplantation and lung-volume reduction surgery (LVRS), have been used to treat patients with advanced disease. Both treatments directly address the problem of hyperinflation but have important limitations. Lung transplantation involves replacement of one or both diseased lungs with an organ from a cadaveric donor, and has been shown to improve pulmonary function, symptoms, functional capacity and quality of life in patients with end-stage emphysema [6,7]. However, lung transplantation is costly, and therapy is available to only approximately 3000 patients annually worldwide due to limited organ availability and access to specialized tertiary care centers. Furthermore, transplantation has no significant effect on mortality in emphysema. Chronic rejection remains a major unresolved problem among patients who undergo lung transplantation, with only approximately half of transplanted patients surviving beyond 5 years [8–10].

Lung-volume reduction surgery has proven beneficial for selected patients with advanced emphysema since it directly addresses the problem of lung hyperinflation through resection of damaged tissue [11,12]. By restoring a more normal structural relationship between the lung and chest wall, volume reduction therapy reduces gas trapping, improves elastic recoil, increases expiratory flows and allows the rib cage and diaphragm to function more effectively. The benefits of lung-volume reduction through surgical resection have been confirmed in single-center studies, and in the multicenter National Emphysema Treatment Trial (NETT), a 1218-patient, randomized, controlled clinical trial performed at 17 centers across the USA [13]. Results from NETT demonstrate that LVRS is an effective therapy for many patients with advanced emphysema, producing improvements in pulmonary function, exercise capacity and quality of life that last for several years [14,15]. It has also been shown to reduce COPD exacerbation frequency and oxygen use [16,17]. In those patients with upper lobe emphysema and limited baseline exercise capacity, LVRS has the greatest benefit. In addition to physiological and functional improvements, these patients experience an improvement in long-term survival. LVRS is the only intervention, other than smoking cessation and oxygen therapy, shown to alter the natural history of this disease [13]. Unfortunately, LVRS is associated with significant morbidity and mortality. In NETT, overall surgical mortality (mortality within 90 days of treatment) was 7.9%, and significant morbidity was observed in approximately 50% of patients [14]. One month following treatment, nearly a quarter of LVRS patients in NETT remained hospitalized for medical care. Thus, despite its potential benefits, fewer than 500 cases of LVRS are performed annually throughout the world [18].

By confirming the physiological and functional benefits of LVRS as well as its risks, NETT spurred interest in nonsurgical methods for achieving lung-volume reduction. Development of effective endobronchial lung-volume reduction therapies that could treat hyperinflation in patients with emphysema without the risks of surgery could fundamentally alter patient management strategies.

Review of the AeriSeal System

Overview of the market

Presently, there are four devices approved in Europe to perform endobronchial lung-volume reduction therapy for the treatment of advanced emphysema (Table 1):

- The Zephyr® EBV Valve System (Pulmonx)
- The IBV® Valve System (Spiration)
- The RePneu™ Lung Volume Reduction Coil (Pneumrx)
- The AeriSeal Emphysematous Lung Sealant System (Aeris)

Endobronchial valves, which were first approved 6 years ago, have been used most extensively. Endobronchial valve therapy, which has been evaluated in several clinical trials and is commercially available in Europe, is designed to produce lung-volume reduction through absorption atelectasis by blocking gas flow into a target area of the lung while allowing gas to exit through the one-way valves that have been positioned in the segmental airway. Valve therapy appears to benefit the cohort of emphysema patients with upper lobe disease who do not have significant collateral ventilation, a pathophysiological condition whereby air can enter alveoli beyond a valve through pathways connecting adjacent segments and even lobes in the diseased lung, rendering the valve ineffective [19]. Because the majority of patients with advanced emphysema have clinically significant collateral ventilation, it is estimated that approximately 20–30% of emphysema patients that have upper lobe emphysema have sufficiently low levels of collateral ventilation to respond favorably to endobronchial valve therapy. There are no published data describing the use of valves in patients with homogeneous

Table 1. Alternative devices.

Product name	Company	Technology	Target patients	Approval status
Zephyr® EBV Valve System	Pulmonx (Emphasys)	Endobronchial valve	Heterogeneous with low collateral ventilation	CE mark approval. Not approved in USA
IBV® Valve System	Spiration/ Olympus	Endobronchial valve	Heterogeneous with low collateral ventilation	CE mark approval. Not approved in USA
AeriSeal® Emphysematous Lung Sealant System	Aeris	Lung sealant	Homogenous and upper lobe-predominant heterogeneous	CE mark approval. Not approved in USA
RePneu™ Lung Volume Reduction Coil (LVRC)	Pneumorx	Endobronchial coil	Heterogeneous	CE mark approval. Not approved in USA

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emphysema. Thus, for patients with upper lobe disease who have excessive collateral ventilation, and for patients with homogeneous disease, alternative therapies are required.

Very limited published data are available regarding the safety and efficacy of airway coils, a second type of mechanical device designed to produce lung-volume reduction in patients with advanced emphysema. Results have demonstrated short-term efficacy in patients with upper lobe-predominant emphysema, which appears to decline after several months [20]. Patients with homogeneous disease did not appear to benefit from therapy.

The AeriSeal System is specifically designed to overcome the problem of collateral ventilation. It is also the only device currently approved for the treatment of patients with advanced homogeneous emphysema. It therefore has the potential to significantly impact clinical management of patients with advanced emphysema who currently have few therapeutic alternatives.

Introduction to the AeriSeal System

The AeriSeal System consists of the following components (Figure 1):

- The Emphysematous Lung Sealant (foam sealant);
- Solution A: 4.5 ml of synthetic polymer consisting of an aqueous solution of chemically modified polyvinylalcohol (PVA) (Figure 1A);
- Solution B: 0.5 ml of buffered crosslinker, which reacts with amine groups on the modified PVA (Figure 1B);
- The catheter (Figure 1D): 107 cm overall length, 100 cm working length, 1.8 mm outer diameter (5.5 F), manufactured from medical-grade blue-colored PEBAX®. The tip of each catheter is marked with a 2 cm black band beginning 2 cm from the top to facilitate visualization;
- The accessories kit (Figure 1C), which contains the administration syringe (a 20 ml polycarbonate syringe fitted with a ring grip and male luer connector) and other commercially available accessories to draw up, mix and administer the device.

All device components are single use and disposable. No investment in capital equipment is required to use the product.

Treatment is administered with the bronchoscope in wedge position, such that the scope is extended to fit snugly against the wall of the airway. The catheter is passed through the working channel of the bronchoscope until its tip extends approximately 4 cm from the tip of the scope. Wedge position is maintained throughout delivery of the foam sealant to prevent spillage of material. Each dose of foam sealant is prepared for administration at the bedside. Solution A is mixed with Solution B and 15 ml of air. A foam is generated by passing the material back and forth through a stopcock between two syringes. The liquid foam sealant is injected over approximately 5 s and polymerizes *in situ*. Wedge position is maintained for 1 min following delivery to allow complete polymerization, during which the liquid foam transforms into a sticky adhesive film. The scope is then repositioned at the next treatment site and the procedure repeated until all treatments have been completed. AeriSeal Foam Sealant is approved for use at up to three subsegments during a single session. Each subsegmental treatment requires 2–3 min to complete.

The AeriSeal System is designed to function at the level of the small airways and alveoli by blocking collateral channels, preventing gas from entering the region and leading to absorption atelectasis. Thus, its efficacy should not be significantly affected by the presence of collateral ventilation. Once the tissue surfaces within the treated area are approximate, the adhesive film seals the area closed to ensure a durable response.

Clinical profile & post-marketing data

The AeriSeal System received CE Mark approval in 2010 based upon the results of two clinical trials conducted in Europe and Israel [21,101]. The first study was performed as on open-label, non-controlled multicenter study at six clinical sites in Germany [21]. In total, 25 patients with advanced upper lobe-predominant emphysema were divided into three groups and received treatment at two, three or four subsegments in one upper lobe during a single treatment session. The primary efficacy outcome measure of the study was change from baseline in gas trapping, measured as residual volume to total lung capacity (RV/TLC) ratio 12 weeks following treatment. Treatment success was *a priori* defined as a statistically significant reduction in group mean RV/TLC ratio. Secondary outcome measures included change from baseline at

Figure 1. AeriSeal® System device components. (A) Solution A, polymer solution; **(B)** Solution B, crosslinker; **(C)** accessory kit; **(D)** administration catheter. Reproduced with permission from Aeris.

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12- and 24-week follow-up in forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), diffusing capacity (DLco), Medical Research Council Dyspnea score (MRCD), exercise capacity measured in terms of 6-min walk test (6MWT) distance, health-related quality of life measured in terms of the St George's Respiratory Questionnaire (SGRQ) total domain score and change from baseline at 24 weeks in RV/TLC ratio. Treatment safety was assessed in terms of adverse events during follow-up. Patients were required to have persistent symptoms despite optimized medical therapy to be eligible for the study. Approximately half of the study participants had participated in pulmonary rehabilitation within 6 months of AeriSeal System therapy.

Therapy was well tolerated when performed under either general anesthesia or conscious sedation. There were no significant procedural or immediate postprocedural complications. During the course of follow-up, AeriSeal System therapy displayed an acceptable safety profile. There were no treatment-related deaths, and adverse events beyond 90 days were rare. Acutely, within the first few days of treatment, the majority of patients experienced an inflammatory reaction associated with mucosal irritation from contact with the foam sealant. This was accompanied by transient fever, shortness of breath, pleuritic chest pain, leukocytosis, elevated C-reactive protein and fibrinogen levels, fever and malaise. The reaction was generally self-limited and resolved within 24–96 h with supportive care. Other serious pulmonary side effects out to 6 months included COPD exacerbations (11), pneumonia (three), bronchitis (one) and hemoptysis (one), the majority of which occurred within 90 days of treatment.

Efficacy results in this initial study were promising [21]. At 6-month follow-up, statistically significant improvements from baseline were observed in FEV_1 (+10.0 ± 19.8%; p = 0.028), FVC (+15.8 ± 22.2%; p = 0.004), RV/TLC (-4.7 ± 9.5%; p = 0.039), and SGRQ (-7.5 ± 14.4 U; p = 0.049). Mean improvements were also observed in MRCD (-0.4 ± 1.20 U; p = 0.161), 6MWT distance (+24.6 ± 58.9 m; p = 0.078) and DLco (+14.4 ± 33.3%; p = 0.081) that were not statistically significant (all testing was performed 30 min following administration of short-acting bronchodilator therapy). According to established ATS/ERS criteria, 55% of patients in the study demonstrated clinically significant improvements from baseline in spirometry at 6 months [22]. The fraction of patients demonstrating improvements in FEV_1 and quality of life at this time point was similar to that reported following LVRS in NETT [13].

Based upon the results of the first study, changes were made to the treatment protocol to further improve safety and efficacy. These changes included administration of a 7-day course of peri-procedural prophylactic antibiotics and steroids, limiting treatment to a single subsegment in each lung segment, and administering the foam sealant more peripherally through distal catheter placement.

A second study was conducted as an open-label, noncontrolled, multicenter study at four hospitals in Germany, one in France, one in Austria and two in Israel [101]. In total, 56 patients were enrolled: 30 with homogeneous emphysema, 19 with heterogeneous upper lobe emphysema and seven with heterogeneous lower lobe emphysema. Patients received initial treatment at two nonadjacent subsegments in the most diseased lobe of the lung, and were eligible for a second treatment session, as determined by the treating physician. In total, 39 of the 56 patients underwent a second treatment session. Primary and secondary efficacy end points were identical to those of the first study. All patients were followed for at least 3 months, and longer-term follow-up is ongoing.

Changes in treatment algorithm after the initial study reduced side effects substantially. Signs and symptoms of inflammation during the first 1–2 days following AeriSeal System treatment decreased by over 60%. Within the first 90 days, the incidence of all-cause COPD exacerbations requiring hospitalization decreased from 44 to 9%, and the incidence of all-cause pneumonia/pneumonitis requiring hospitalization decreased from 16 to 1.8%.

Subgroup analysis of efficacy results from the study identified pretreatment patient characteristics predictive of the best responses to therapy. This analysis demonstrated that patients with DLco between 20 and 60% predicted who received treatment in the upper lobes did particularly well, whether they had homogeneous or heterogeneous disease. Conversely, patients treated in the lower lobes failed to improve with therapy.

Among patients with homogeneous disease and DLco between 20 and 60% of predicted who received unilateral upper lobe therapy, post-bronchodilator responses at 12 weeks were very good, with improvements in gas trapping (ΔRV/TLC = -7.6 ± 7.9%; p = 0.006), spirometry (ΔFEV_1 = +17.0 ± 14.4%; p = 0.002; ΔFVC = +12.5 ± 14.2%; p = 0.01), 6MWT distance (+2.0 ± 74.5 m; p = 0.93), MRCD scores (-0.1 ± 1.0 U; p = 0.78) and health-related quality of life (ΔSGRQ total domain score = -12.8 ± 14.8 U; p = 0.02). Among patients with upper lobe-predominant heterogeneous emphysema and DLco between 20 and 60% predicted who received bilateral upper lobe therapy, post-bronchodilator responses at 12 weeks were even better. Improvements in gas trapping (ΔRV/TLC = -14.9 ± 5.3%; p = 0.001), spirometry (ΔFEV_1 = +26.0 ± 41.8%; p = 0.12, ΔFVC = +23.2 ± 26.7%; p = 0.04), 6MWT distance (65.1 ± 80.1 m; p = 0.04), MRCD scores (-0.7 ± 0.71 U; p = 0.02) and health-related quality of life (ΔSGRQ total domain score = -9.2 ± 10.5U; p = 0.03) were similar to those reported following LVRS in patients with upper lobe disease [23–25]. Long-term follow-up for participants in this study are currently pending.

Patient selection and treatment algorithms for identifying the best candidates for AeriSeal System therapy are currently being evaluated prospectively. Aeris is conducting a multicenter trial in Israel examining bilateral four-site single session therapy of patients with advanced upper lobe and homogeneous emphysema with DLco 20–60% predicted. The study is ongoing and results are expected in the latter part of 2011.

Current status in the medical field

The AeriSeal Emphysematous Lung Sealant System is approved in Europe for the treatment of advanced emphysema. Aeris currently recommends that only patients with upper lobe predominant or

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homogeneous emphysema with DLco 20–60% and target sites in the upper lobes be treated. This subset of patients represents a significant expansion over the group believed to benefit from other endoscopic volume reduction devices. If initial results from Aeris' clinical trials demonstrating safety and efficacy in patients with advanced upper lobe as well as homogeneous emphysema are confirmed, and long-term benefit demonstrated, AeriSeal System therapy will address a critical unmet need by providing pulmonologists, interventionalists and thoracic surgeons with a simple endoscopic therapy to improve lung function and quality of life in the majority of patients with advanced emphysema, independent of whether or not they have collateral ventilation.

Conclusion

AeriSeal System Emphysematous Lung Sealant is a novel endoscopic lung-volume reduction system that has recently entered the commercial market in Europe. The device was approved based upon favorable results from two uncontrolled clinical trials [21,101]. Despite small patient numbers, statistically significant improvements were observed in all study outcome measures for the combined cohort of patients for which CE Mark registration was approved – those with homogeneous and heterogeneous upper lobe emphysema.

Treatment is simple to administer and procedure times are short relative to other endoscopic volume reduction device procedures. Although data are limited, benefits have been observed beyond 6 months. Long-term follow-up up to 1 year is ongoing. Theoretically, treatment should produce effective volume reduction independent of collateral ventilation, although this had not been demonstrated through direct measurements of collateral ventilation in patients undergoing therapy. The safety profile of the AeriSeal System has improved with clinical experience and protocol changes. The incidence of COPD exacerbations within the first 90 days of therapy is approximately equivalent to that observed with endobronchial valves.

Expert commentary

The AeriSeal System offers the potential to successfully treat many more patients with advanced emphysema than can be treated with currently existing therapies. The simplicity of the procedure allows even first-time users without extensive interventional experience to perform the procedure safely and effectively. As with all such treatments, patient and treatment site selection are key to successful therapy. Aeris has developed simple guidelines to assist with this process; however, these guidelines have yet to be validated prospectively.

While confirmation of efficacy outside of clinical trials remains to be demonstrated, the ability to treat patients with homogeneous disease and upper lobe disease independent of collateral ventilation is unique to this product. These features represent significant advances in the field of endoscopic lung-volume reduction.

Five-year view

Aeris is currently performing an investigational trial in Israel to examine the safety and efficacy of single session four-site therapy in patients with advanced upper lobe and homogeneous emphysema and DLco 20–60%. Results from the trial will be available in the second half of 2011. Additional clinical data is also expected within the next several years on the RePneu coils, which, like the AeriSeal System, may be less sensitive to collateral ventilation.

Information resource

Additional information about the AeriSeal System is available on Aeris' website: www.aeristherapeutics.com.

Financial & competing interests disclosure

Edward P Ingenito is the chief medical officer at Aeris Therapeutics and has a financial interest in the company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- A large unmet need exists for effective endobronchial lung volume reduction treatments in patients with advanced emphysema.
- The efficacy of endobronchial valves is limited by the presence of collateral ventilation.
- The AeriSeal® Emphysematous Lung Sealant System is a recently approved endobronchial lung volume reduction system commercially available in Europe for treatment of advanced emphysema.
- The AeriSeal System is designed to produce therapeutically effective lung-volume reduction independent of the extent of collateral ventilation.
- Patients with upper lobe-predominant or homogeneous emphysema are candidates for treatment.
- Treatment is simple to perform under either general anesthesia or conscious sedation.

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Website

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