

**February 28, 2003 Meeting of the
General and Plastic Surgery Devices Advisory Panel**

Background Information: Devices for Treatment of Emphysema

Emphysema is a condition of the lung characterized by abnormal permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls in the absence of obvious fibrosis. The cardinal physiologic defect in emphysema is a decrease in elastic recoil. This results in decreased maximum expiratory airflow, hyperinflation and air-trapping. Emphysema is usually the result of cigarette smoking, and it is a chronic progressive disorder that ultimately leads to disability and early death. It is estimated to be present in 2 million adults in the United States and along with other forms of chronic obstructive pulmonary disease (COPD) accounts for > 90,000 deaths annually¹.

The American Thoracic Society has promulgated guidelines for the diagnosis and management of emphysema.² The goals of therapy are to halt the progressive decline in lung function, prevent and shorten the exacerbations of the disease, improve exercise capacity and quality of life and improve survival. Medical management has included pulmonary rehabilitation (aerobic exercise conditioning, education, psychosocial support), use of bronchodilators and long-term domiciliary oxygen therapy. In patients with far-advanced COPD, single or double lung transplantation has been used in some cases, but this option is limited by the availability of donor organs.¹⁻²

A surgical treatment that is currently under study is lung volume reduction surgery (LVRS). This involves surgical excision of lung tissue to reduce the volume of the hyperinflated lung parenchyma. The National Emphysema Treatment Trial (NETT) is a multicenter, randomized clinical trial of 2500 patients and will study medical therapy vs medical therapy plus lung volume reduction surgery for the treatment of patients with severe bilateral emphysema¹. In this trial that is currently underway, patients will complete a 6 to 10 week course of pulmonary rehabilitation prior to randomization and will participate in a maintenance program of pulmonary rehabilitation after randomization. The primary endpoint for the NETT trial is survival. Additional outcomes include maximum exercise capacity, pulmonary function, oxygen requirement, distance walked in 6 minutes (the so called "6 minute walk test" or 6MWT), quality of life, respiratory symptoms and health care utilization and costs. The study duration is 4.5 years.

The inclusion criteria for the NETT include: (1) radiographic evidence of bilateral emphysema (2) severe airflow obstruction and hyperinflation (3) participation in pulmonary rehabilitation with the attainment of preset performance goals. The exclusion criteria are (1) high risks for perioperative morbidity (2) disease considered unsuitable for LVRS (3) medical conditions making it unlikely that the patient would be able to complete the trial. Preliminary results have indicated that caution is warranted in the use of LVRS for patients who have a low FEV₁ and either homogenous emphysema or a very

low carbon monoxide diffusing capacity. These patients are at a high risk for death after surgery and are unlikely to benefit³.

Recently, there has been some interest in developing devices to achieve some of the same effects as LVRS. Device designs discussed in the literature include the use of fibrin-based glue⁴, occluded stents, medical adhesives⁵, and intrabronchial valves⁶. These devices are designed to be placed using a bronchoscope, thus providing a less invasive treatment than LVRS. In theory, the devices may function by causing a portion of the lung to collapse, thus reducing the total lung volume. Other devices may function by reducing the volume of dead space in the lung. Although the technology of the devices and the mechanism by which they function may differ, they share many similarities. They are permanent implants, placed in the lung using a bronchoscopic approach that are intended to improve the functional status of patients with emphysema.

The FDA has scheduled this panel meeting to discuss some of the clinical trial issues concerning these new technologies. When discussing the questions below, please consider whether the recommendations given apply to the treatment of both heterogeneous and homogeneous emphysema.

Questions for the Panel to consider:

1. What is the appropriate control group for a clinical evaluation of these devices? For example, for which patients would LVRS be an appropriate control group, and for which patients would medical management be an appropriate control group?
2. Clinical trials for these devices will be required to demonstrate safety. Please comment on what you believe to be the most important safety parameters to be evaluated in clinical trials of these devices (e.g., rehospitalization, COPD exacerbation, air leak, pneumonia, infection, hemoptysis, respiratory failure, death).
3. Clinical trials for these devices will also be required to demonstrate effectiveness. Please discuss the merits of each of the parameters below as well as any other parameters that you believe to be important to demonstrating device effectiveness. When possible, please discuss the degree of improvement or decline that would be clinically significant for these or other parameters (e.g., an increase in how many feet in the 6MWT is a significant improvement).
 - a. Pulmonary function (FEV₁)
 - b. 6 minute walk test
 - c. Maximum exercise capacity
 - d. Quality of Life (SF-36)
 - e. Dyspnea questionnaires
 - f. Length of hospital stay

4. The duration of follow-up should allow FDA to adequately assess the safety and effectiveness of these permanently implanted devices in a chronically ill population. Please comment on what you believe to be the appropriate duration of follow-up for a pivotal clinical study for these devices.

References

1. Rationale and Design of the National Emphysema Treatment Trial: A Prospective Randomized Trial of Lung Volume Reduction Surgery, Chest, 116:6, 1999, pp. 1750-1761.
2. Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease, Am. J. Respir. Crit. Care Med., 152, 1995, pp.S77-S120.
3. Patients at High Risk of Death After Lung-Volume-Reduction Surgery, N. Eng. J. Med., 345:15, 2001, pp. 1075-1083.
4. Ingentio, et al., "Bronchoscopic Lung Volume Reduction: A Safe and Effective Alternative to Surgical Therapy for Emphysema" Am. J. Respir. Crit. Care Med., 164, 2001, pp.295-301.
5. Toma, T.P., "The Flexible Bronchoscopic Approach to Lung Volume Reduction", Pneumologia, Vol L., Nr. 2, 2001, pp.100.
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