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Clinical Study Protocol

Balloon-expandable Metallic Stents for Airway Diseases

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Stent placement is an essential treatment for airway diseases. Although self-expandable metallic stents and silicone stents are commonly applied for the treatment of airway diseases, these stents are unsuitable for the treatment of small airway diseases encountered in pediatric patients and lung transplant recipients with airway complications. Currently, only vascular balloon-expandable metallic stents are available for the treatment of small airway diseases; however, little research has been conducted on the use of these stents in this field. We have launched a prospective feasibility study to clarify the safety and efficacy of balloon-expandable metallic stents for the treatment of airway diseases.

Key words: metallic stent, airway disease, lung transplantation, airway complication, airway malignancy

Small airway diseases requiring surgical intervention are generally treated with surgery in operable patients. However, in some cases, such as inoperable patients, pediatric patients, and lung transplant recipients with airway complications, bronchoscopic intervention including airway stenting is suitable. Among these situations, airway complications after lung transplantation (LT) could be life-threatening [1-3], necessitating careful treatment with bronchoscopic intervention. In living-donor lobar LT, which is an established alternative to solve donor shortages exclusively in Japan, airway complications commonly develop in the lobar to segmental bronchi, since the right and left lower lobes from two healthy donors are implanted in the recipient in place of the whole lungs. These lesions are small both in diameter and length, necessitating small airway stents. Although various types of airway stents, including self-expandable metallic stents, silicone stents and biodegradable stents, are currently applied for patients with airway diseases [4-7], these types of airway stents are often too large to fit inside small airways.

Similar to the airway complications after living-donor lobar LT, congenital tracheal stenosis in pediatric patients is a small airway disease that can be treated using small airway stents. For the treatment of congenital tracheal stenosis, a balloon-expandable metallic stent (BEMS) has been shown to provide favorable short- and long-term outcomes [8-10]. In general, BEMS is used as a vascular stent for peripheral blood vessels, such as the femoral artery and the renal artery, and its safety as a vascular stent is described previously [11-14]. Accordingly, BEMS is smaller than conventional airway stents and can also be safely and easily deployed using a bronchoscope [8-10,15]. Despite advisories to restrain from using metallic stents for the treatment of benign airway diseases [16], airway complications after LT have been treated with self-expandable metallic stents [6,7], since immunosuppression therapy after lung transplantation can inhibit granulation tissue formation in the

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metallic stents [17]. Only BEMS is currently available for the treatment of small airway diseases; therefore, BEMS could be a valuable treatment option for airway complications after living-donor lobar LT as well as for pediatric airway diseases and airway malignancies in inoperable patients [18,19]. However, few studies have examined the safety and efficacy of BEMS for the treatment of airway diseases, prompting us to launch the current study.

Endpoints

The present study will evaluate the efficacy and safety of BEMS for the treatment of airway complications after LT, pediatric airway diseases, and airway malignancies. The primary endpoint will be the clinical success rate (calculated as the ratio of the number of patients with clinical success to the number of registered patients) on the first postoperative day. The secondary endpoints will include the re-stenosis rate, adverse event rate, overall survival (OS), clinical symptoms, pulmonary function, the location of the stent placement, and the number of stents used during the follow-up period, which will consist of 5 to 10 years, depending on the timing of patient registration in this study.

Study Design

We have launched a single arm, prospective, non-randomized, uncontrolled, open label, single-center study. The trial is registered at UMIN clinical trials registry, Japan (UMIN000015197). Fig. 1 shows an overview of the study design.

Eligibility Criteria

All the patients who meet the main inclusion and

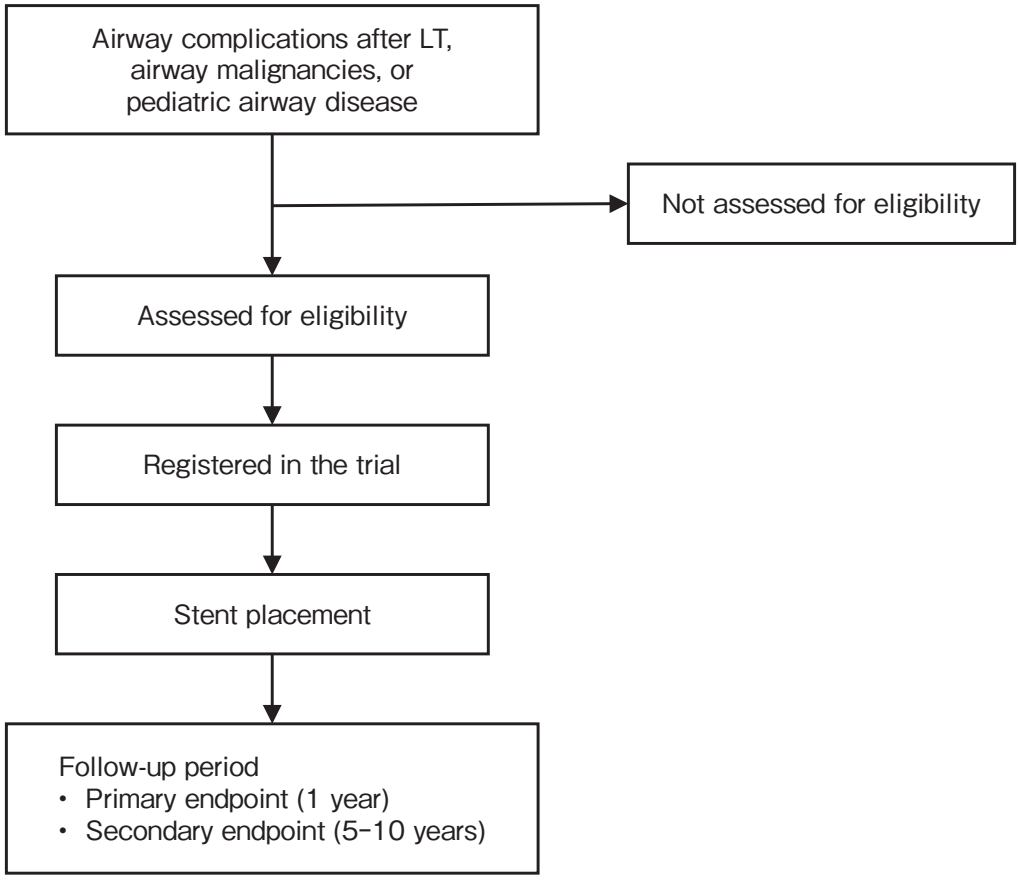

Fig. 1 Overview of the study design. LT, lung transplantation.

Table 1 Patient eligibility

Inclusion criteria
1) Airway complications after lung transplantation, airway malignancies, or pediatric airway diseases
2) Airway diseases confirmed using chest CT or bronchoscopy
3) No indications for other surgical treatments or conventional airway stenting
4) Adequate hemopoietic functions as follows: leukocytes $\geq$ 2,000/μL, platelets $\geq$ 30,000/μL, hemoglobin $\geq$ 6.0 g/dL
5) Patients can be included regardless of whether they have a history of airway stent placement
Exclusion criteria
1) Severe myelosuppression, renal injury or liver injury
2) Broncho-esophageal or broncho-vascular fistula
3) Contraindications for bronchoscopy
4) Severe heart diseases
5) Severe mental diseases
6) Other factors making the individual unsuitable for enrollment in the study

exclusion criteria will be invited for screening. The main inclusion and exclusion criteria are listed in Table 1. This study was conducted in compliance with the principles of the Declaration of Helsinki, and the study protocol has been approved by the institutional review board of Okayama University Hospital (No. m12006).

Treatment Methods

Screening will be performed within 7 days before stenting. After admission to our hospital on the day before stenting, the BEMS will be placed in position using a rigid or fiberoptic bronchoscope while the patient is under general anesthesia. First, a guide wire will be passed through the target airway lesion, and the lesion will be dilated with a balloon catheter if required. Next, depending on the diameter of the lesion as estimated using chest computed tomography (CT), an Express Vascular SD stent or an Express Vascular LD stent (Boston Scientific Japan Co., Tokyo, Japan) mounted on another deflated balloon catheter (the stent delivery catheter) will be positioned within the lesion. The exact site for the stenting will be determined by the simultaneous use of bronchoscopy and fluoroscopy. Finally, the balloon on the stent delivery catheter will be inflated, allowing the stent to expand in size in the proper position. All the patients will be followed for 5 to 10 years after stenting. All the procedures will be performed with an adequate understanding, and written informed consent will be obtained from the patient by an investigator before any screening or inclusion procedures are performed.

Statistical Consideration

For the primary endpoint, clinical success will be defined as follows: confirmation of the re-opening of the airway lesion using a bronchoscope immediately after stent placement, and confirmation of stent patency using a chest radiograph taken on the first postoperative day. For the secondary endpoint, re-stenosis will be assessed using chest CT examinations during the follow-up period. An OS curve will be constructed using the Kaplan-Meier product-limit method and GraphPad Prism (GraphPad Software, CA, USA).

We assume that 30 patients will be registered in this study. Based on the number of LT cases treated at our hospital, 100 LT cases will likely be performed during the 5-year period until September 30, 2019; according to our historical data, 10% of LT recipients (10 patients) are likely to develop airway complications [20,21]. In addition, 10 former LT recipients are likely to encounter airway complications, and 10 patients with other airway diseases are likely to require stent placement during the registration period.

This study will be performed between September 17, 2014, and September 30, 2024.

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