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BRIEF COMMUNICATION

Lung transplant airway complications treated with biodegradable airway stents: The Dutch multi-center experience

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Abstract

Introduction: Treatment of post lung-transplant airway complications is challenging, and treatment with conventional airway stents is associated with adverse events. More recently, biodegradable airway stents (BDS) have been introduced and may be used to reduce these adverse events. In this study we explore the feasibility of treatment with BDS post lung transplant.

Methods: All patients treated with BDS in The Netherlands were included in this retrospective multicenter study. Feasibility, life span of the stent, occurrence of adverse events, and evolution of lung function were evaluated.

Results: Twelve patients (six malacia and six stenosis) received a total of 57 BDS, ranging from 1 to 10 BDS per patient. Six patients had been pretreated with conventional airway stents. Median stent life span was 112 days (range 66–202). No adverse events occurred during stent placement. In 5 out of 57 stent placements, a single additional bronchoscopy was necessary because of mucus accumulation ($n = 4$) or excessive granulation tissue ($n = 1$). All stent naïve patients became airway stent independent after treatment; all patients pretreated with conventional airway stents were still airway stent dependent at the end of follow up.

Conclusion: Treatment with BDS is safe and feasible. Adverse events were mild and easily treatable. All patients with initial treatment with BDS were airway stent independent at the end of follow up with a median treatment of 4 BDS.

KEYWORDS
airway complications, airway stent, biodegradable airway stent, lung transplant

1 | INTRODUCTION

Treatment of post lung-transplant (LTx) airway complications (AC) has been a major clinical challenge since the introduction of human LTx.[1] AC, consisting of necrosis, stenosis, malacia and dehiscence, affect 2%–18% of all post LTx patients.[2] The approach is primarily conventional treatment with clearing out airway debris and balloon dilatation before other conventional therapeutic options as laser treatment, electrocautery, or cryotherapy.[3,4] In severe cases of dehiscence, malacia or stenosis, airway stent placement can be necessary. However, this is

usually considered a last resort given the potential complications and side effects of airway stents and the lifetime maintenance.

The most widely used airway stents are silicone stents or self-expandable metallic stents (SEMS), with the latter bare metal, partially covered or fully covered. Each with their own challenges.

Silicone stents are placed using rigid bronchoscopy under general anesthesia. Post Ltx series show considerable adverse events as migration (41%), mucus accumulation (41%), and obstructive granulomas (59%).[5,6] Their lesser adaptability in angulated target lesions, or significant changes in airway dimensions makes them less attractive for longer annulated sites.[7] Yet, they have shown to be feasible post LTx AC.[5,8]

SEMS are commonly used in AC, but have alike limitations. Airway granulation in reaction to foreign[9,10] can cause restenosis in up to 52% of the cases. Bacterial airway colonization occurred in 40% of a retrospective series.[11,12] Another disadvantage of the metallic stents is difficulty of removal after a longer period in situ.[13] However, this mainly applies to uncovered stents which, after an FDA public health notification in 2005 are no longer recommended for benign disease.[14]

The limitations of the currently available stents necessitate innovative solutions to improve the management of post LTx AC. An interesting new development in this respect is the fully biodegradable stent (BDS). BDSs have proven to be useful in esophageal stenosis treatment[15] and small series have shown feasibility in post lung transplant AC.[16–18] Biodegradable airway stents are made from polydioxanone which is an absorbable polymer and the stents are noncovered. A major advantage is that removal of the stent is unnecessary, and ciliary structure remains preserved. In animal models they have proven to hold radial strength for about 6 weeks.[19]

The primary aim of this study was to assess safety and feasibility of BDS in LTx. Safety was assessed regarding placement and occurrence of stent related adverse events and feasibility was assessed as the performance of the BDS in post LTx AC, the need for bronchoscopic interventions and the short- and long-term effect on lung function.

2 | METHODS

This was a multicenter retrospective study of all post Ltx patients who have been treated with a biodegradable airway stent between April 2019 and April 2022 for an AC of the anastomosis or distal airways, during this period approximately 300 lung transplants were performed in the Netherlands. Included patients were treated in the University Medical Center Groningen (n = 9) and the Amsterdam University Medical Center (n = 3). All patients had been referred from one of three lung transplant centers in the Netherlands. For all patients, stent placement was only resorted to in the event of refractory symptoms after conventional therapy for example (repetitive) balloon dilatation, electrocoagulation of argon plasma therapy.

Patient demographics, LTx indication, localization of AC, lung function data before and after all BDS stent placement (FEV_1 and FVC) and intervention bronchoscopy details were retrieved using a predefined case report file using Redcap software (Redcap, Nashville, United states). If patients had been treated with conventional airway stent prior to the BDS, this data was also obtained. All patients had provided written informed consent for transplant-related research and the study was approved by the local ethics committee (METc 2022/185). The study was registered at clinical trials under NCT05334199.

Intervention bronchoscopy for stent placement was performed under general anesthesia using rigid or flexible bronchoscopy depending on the individual case. Commercially available BDSs (ELLA-CS Ltd, Czech Republic) were used. All were manufactured on clinical prescription. If applicable, prior used SEMS were Ultraflex (Boston scientific Corp, USA), Taewoong Niti-s (Taewoong Medical, Korea) or custom made Leufen Aerstent (Leufen Medical, Germany).

Continuous data are expressed as median ± range. Ordinal variables are expressed as percentages. Because data did not fulfill conditions for normal distribution, Mann–Whitney U test was used for continuous data and Fishers exact test for ordinal parameters. All analyses were conducted with IBM SPSS Statistics version 24 (IBM, NY, USA).

3 | RESULTS

3.1 | Baseline characteristics

A total of 12 patients (42% female) underwent BDS placement for AC post LTx and were included. Indication for LTx was chronic obstructive pulmonary disease (n = 4), cystic fibrosis (n = 3), interstitial lung disease (n = 3), pulmonary hypertension (n = 1) and pulmonary manifestation of graft versus host disease after stem cell transplantation for acute myeloid leukemia (n = 1). Six patients had airway stenosis and six patients had airway malacia. Location of BDS placement was in the left main bronchus (n = 8), right main bronchus (n = 2) and bronchus intermedius (n = 2). Median age at the time of first stent placement was 63 years (range 32–68). See Table 1 for all patient characteristics.

3.2 | Biodegradable stent placement procedure

In total 57 BDS were placed, ranging from 1 up to 10 (median 4) consecutive stent placements per patient. Indication for new stent placement was dissolving of the stent with persisting of the malacia of stenosis. No adverse events occurred during stent placement, all attempts for stent placement succeeded. Five (8.8%) stent associated adverse events occurred, consisting of four stent obstructions due to sputum stasis and one case of excessive granulation tissue just proximal of the stent. All adverse events could be resolved with a single additional regular bronchoscopy. In the case of excessive granulation tissue this was resolved with electrocoagulation, all other complications were resolved with suction of sputum. No stent migration occurred. Median time between first and last BDS placement was 13 months (range 0–35 months). Median time until the next stent placement was 112 days (range 66–202 days). Six (50%) patients were stent-naïve prior to BDS airway stent treatment, and six (50%) patients had been treated with a conventional airway stent prior to BDS treatment.

TABLE 1 Patient characteristics.

Patient	Age	Sex	Primary disease	Type of AC	Site AC	Conventional stent (months)	Total BDS	Treatment completed at end follow up	Adverse event BDS
With prior conventional stent treatment									
1	40	M	CF	Malacia	LMB	SEMS (111)	4	No	
2	33	M	GvhD	Malacia	LMB	SEMS (47)	10	No	
3	33	F	CF	Stenosis	LMB	SEMS (33)	7	No	2x SS
4	32	M	CF	Stenosis	LMB	SEMS (217)	2	No	1x SS
5	65	M	COPD	Malacia	RMB	Silicone (11)	3	No	1x EGT
6	62	F	ILD	Stenosis	LMB	SEMS (48)	7	No	
Without prior conventional stent treatment									
7	67	M	ILD	Stenosis	RMB	N.A.	4	Yes	1x SS
8	68	F	PH	Stenosis	BI	N.A.	4	Yes	
9	55	M	COPD	Malacia	LMB	N.A.	9	Yes	
10	63	F	COPD	Malacia	BI	N.A.	5	Yes	
11	66	M	COPD	Malacia	LMB	N.A.	1	Yes	
12	67	F	ILD	Stenosis	LMB	N.A.	1	Yes	

Abbreviations: BI, bronchus intermedius; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; EGT, excessive granulation tissue; F, female; GvhD, graft versus host disease; ILD, interstitial lung disease; LMB, left main bronchus; M, male; NA, not applicable; PH, pulmonary hypertension; RMB, right main bronchus; SEMS, self-expandable metallic stent; SS, sputum stasis.

3.3 | Patients with prior conventional stent treatment

In the group of six patients with prior treatment with a conventional airway stent, five had been treated with SEMS and one with a silicone stent. Indication for treatment was malacia (n = 3, 50%) and stenosis (n = 3, 50%). The median period of treatment with a conventional stent in this group was 48 months (range 11–217 months). Median time to conventional stent related complication was 27 months (range 0–211 months). Conventional stent related adverse events occurred in all 6 patients. 4/6 patients experienced recurrent in stent granulation and restenosis of the airway, 2/6 patients experienced stent migration (1 Silicone, 1 SEMS) and in 5/6 difficulty of stent removal occurred. 5/6 patients experienced infectious complications. Of these infectious complications, 3/5 were with *Aspergillus fumigatus* and *Pseudomonas aeruginosa*, 1 with *P. Aeruginosa* and 1 with *A. fumigatus*.

Median time from lung transplant to first BDS was 87 months (range 21–221 months). Median time from first conventional stent to the first BDS was 49 months (range 12–217). From the occurrence of the first adverse event related to conventional stent placement, a mean of 10.0 (SD 6.8) bronchoscopic interventions per year were necessary, after BDS this was a mean of 8.7 (SD 5.8) (p = .470).

Median time of treatment with BDS in this group was 15 months (range 3–31 months) and median number of BDS was 6 (range 2–10). All six patients were still airway stent dependent at the end of follow up.

3.4 | Conventional airway stent naïve patients

In the six patients without prior treatment with airway stent, the indication for treatment with BDS was malacia (n = 3, 50%) and stenosis (n = 3, 50%). Median time from lung transplant to first BDS was 4 months (range 3–19 months). Median treatment in this group was 13 months (range 0–25 months) and median number of BDS was four (range 1–9). During treatment with BDS, a mean of 5.3 (SD 1.6) bronchoscopic interventions per year were required (including BDS placement). There was no significant difference in the number of endoscopic interventions between the conventional stents and the primary treated BDS patients (p = .105). No adverse events with new airway colonization or stent related infection occurred.

All six conventional airway stent naïve patients were airway stent independent at the end of follow up. Figure 1 shows a case example of a patient treated with BDS.

3.5 | Pulmonary function

Compared to post lung transplant, but pre stent treatment baseline, median δFEV_1 was +44% (range +18 to +233%, p = .007) after the first BDS stent placement and +68% (range −32 to +121%, p = .016) after the last BDS (Figure 2). Median delta FVC was +21% (range −21 to +103% p = .73) after the first BDS stent placement and +65% (range −35 to 79%, p = .33) after the last BDS.

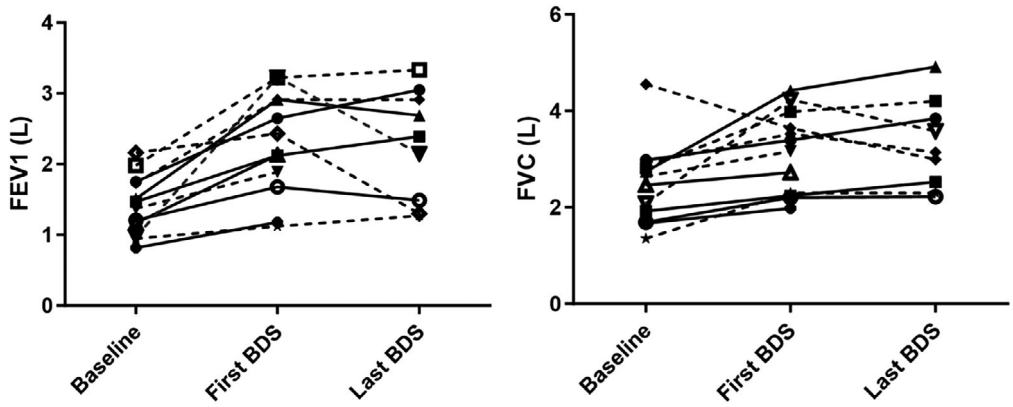

FIGURE 1 Individual patient outcome compared to baseline after first biodegradable stent and last biodegradable stent ($n = 12$). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; BDS, biodegradable airway stent. Interrupted lines are stent naïve patient, solid lines are patients previously treated with conventional stent.

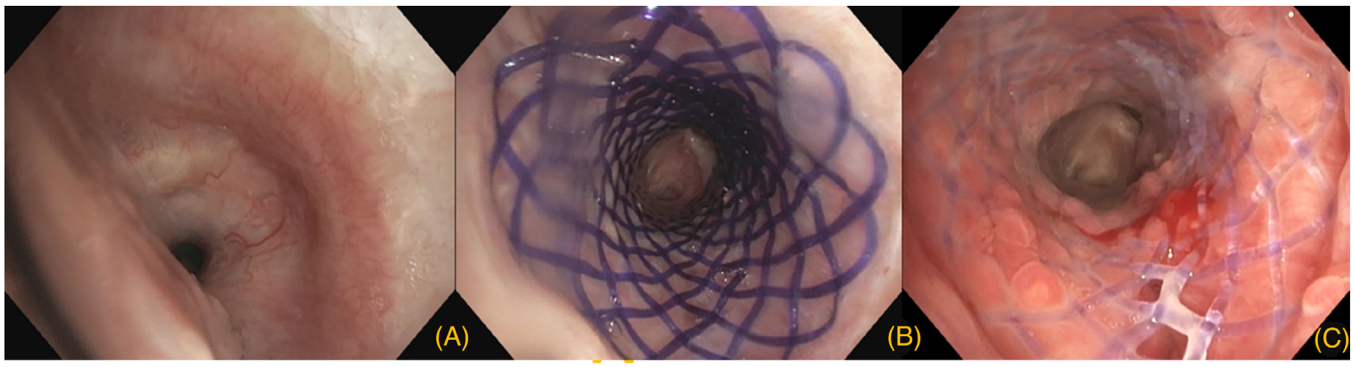

FIGURE 2 Endobronchial status in patient 3 during flexible bronchoscopy. (A) Severe circular malacia of the left main bronchus prior to stent treatment. (B) Treatment with BDS (size 14 × 30 mm) of the left main bronchus. (C) Situation 7 weeks post treatment.

Decrease in FEV_1 and FVC between pretreatment and last airway stent occurred in 1 patient, this due to the development of a severe bronchomalacia on the contralateral side.

3.6 | Survival

Three patients died during follow up, one because of chronic lung allograft dysfunction (CLAD), one because of intrapulmonary manifestation of Kaposi sarcoma caused by a primary HHV-8 infection and one of complications after a re lung-transplant for CLAD.

4 | DISCUSSION

This study, with the placement of 57 biodegradable airway stent in 12 patients shows the feasibility of the use of biodegradable airway stents for patients with post LTx AC. To our knowledge, this is the largest post-transplant series with this type of airway stent. In total 5 (8.8%) adverse events occurred, all of which could be remedied with a single bronchoscopic intervention. No increase of bronchoscopic interventions was observed after start of treatment and all conventional stent naïve patients were airway stent independent at the end of follow up. FEV_1 improved significant after first BDS stent treatment which persisted until the last treatment.

Treatment of post LTx AC with airway stent remains very challenging.[20] As Guibert et al.[21] stated in 2020. The ideal airway stent should be easy to place and remove, large enough to maintain position and not too large to avoid excessive granulation tissue, flexible enough to mimic airway physiology but sufficient radial force to resist airway compression, and not impair mucocilliairy clearance. Potentially, BDS meets all these requirements.

Placement of BDS is relatively easy with flexible bronchoscopy, although under general anesthesia. Stent migration was not observed, and only one case (1.7%) of excessive granulation tissue was observed. Because of the uncovered structure, mucocilliairy clearance still occurs. In only 7% of the cases a single intervention was required because of sputum impaction. Considering the positive and lasting positive impact on lung function this indicates that radial strength is sufficient.

Though it meets almost all [20] standards, the major positive feature of BDS is also its main limiting factor, the stents dissolve. This study shows a mean life span of 112 days until fully dissolving, which means for chronic treatment it is a labor intensive and expensive treatment. However, the same applies for complicated course with conventional airway stents. Future developments will have to show whether stents with will come available with a longer life span. We did not observe more frequent necessity for bronchoscopic interventions compared to the group of conventional airway stents (mean 7.00 vs. 10.0/year, $p = .174$). A potential important advantage is that after completement of treatment with BDS, the cause for interventions has been resolved and the need for interventions declines afterwards.

An important finding is that in all patients with initial treatment with BDS, the treatment was temporary, and patients were airway stent independent at the end of follow up with median treatment of 4 BDS. This is in contrast with the patients previously treated with conventional stents. This group was still stent dependent at the end of follow up. with early BDS treatment, a period of airway recovery may be bridged without the need for permanent airway stenting. In contrast to patients with chronic airway damage that seems irreversible. Therefore, there is low threshold for BDS treatment as primary treatment early post LTx, since it is a temporary and potentially the underlying problem may be overcome. Hence, it has become the first choice airway stent in our clinical practice. Prospective studies with a larger patient sample will have to confirm this finding.

5 | CONCLUSION

Biodegradable airway stents seem suitable for the treatment of post LTx AC. In this case, series minor adverse events occurred, no increase in bronchoscopic interventions and lasting improvement of lung function was observed. The use of Biodegradable airway stents could lower the threshold for airway stent treatment resulting in fewer morbidities in the long term.

AUTHOR CONTRIBUTIONS

Roel van Pel: Writing of the paper. Roel van Pel, Tji Gan, Dirk-Jan Slebos, Karin Klooster, Johannes M.A. Daniels: Participated in research design. Roel van Pel, Tji Gan, Dirk-Jan Slebos: Participated in conducting of the research. Johannes M.A Daniels, Merel E. Hellemons, Dieuwertje Ruigrok: input case studies. Tji Gan, Dirk-Jan Slebos, Karin Klooster, Johannes M.A. Daniels, Merel E. Hellemons and Dieuwertje Ruigrok Participated in review of the paper.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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