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Endobronchial coil treatment in severe emphysema patients with alpha-1 antitrypsin deficiency

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Abstract: Endobronchial coil treatment (ECT) is a minimally invasive procedure developed for palliative care of patients with severe emphysema. ECT has demonstrated a decrease in hyperinflation, an improvement in quality of life, and an acceptable safety profile in randomized controlled trials (RCTs). Because alpha-1 antitrypsin deficiency (AATD) is a classical exclusion criterion in RCTs, there is no available data for ECT in AATD. In this post hoc analysis of the REVOLENS study (Réduction volumique endobronchique par spirales; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01822795) Identifier: NCT01822795), a multicenter 1:1 RCT which compared bilateral ECT with usual care in severe emphysema, we analyzed the efficacy and safety results at 1 year in six patients with AATD (five males, one female; mean age: 52±9 years) who underwent ECT. A significant decrease in hyperinflation (0.35 L decrease in residual volume [RV]) was observed in four out of six patients at 6 months and three out of six patients at 12 months, and an improvement in quality of life (improvement of 4 points in the St George's Respiratory Questionnaire [SGRQ]) was observed in four out of six patients at both 6 and 12 months. Efficacy results at 6 and 12 months from the six AATD patients were compared with 84 non-AATD patients who underwent ECT, and no statistically significant differences were found for FEV₁, RV, 6MWT score and SGRQ score. Respiratory-related serious adverse event was limited to pneumonia in one AATD patient at 1 year post-ECT. This post hoc study suggests that AATD patients may have similar efficacy and safety outcomes at 1 year as non-AATD patients. Because of the paucity of available data, appropriately powered studies are needed to determine the effects of ECT in AATD.

Keywords: COPD, volume reduction, interventional, bronchoscopy

Introduction

Despite optimal medical management including intravenous alpha-1 antitrypsin (AAT) augmentation therapy, many patients with AAT deficiency (AATD) with severe emphysema remain symptomatic.¹ Compared with non-AATD-related emphysema, lung volume reduction surgery is associated with inferior outcomes and lung transplantation is associated with similar outcomes in AATD emphysema.² Endobronchial lung volume reduction (ELVR) treatments including valves, coils, and thermal vapor ablation have demonstrated efficacy and safety in randomized controlled trials (RCTs) including highly selected emphysematous patients.³ However, AATD emphysema is a usual exclusion criterion in RCTs, which has led to the absence of robust data in this population. The REVOLENS study (Réduction volumique endobronchique par spirales; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01822795) Identifier: NCT01822795) is the only one RCT which included AATD patients. In this post hoc analysis of the REVOLENS study, we specifically analyzed the 1-year efficacy and safety outcomes of endobronchial coil treatment (ECT) in AATD patients.

Methods

REVOLENS is a multicenter 1:1 RCT which compared bilateral coil treatment with usual care in 100 patients with severe emphysema, and showed a decrease in hyperinflation, an improvement in quality of life, and an acceptable safety profile at 1 year.⁴ The main inclusion criteria in the REVOLENS study were bilateral emphysema, FEV₁ of less than 50% predicted, residual volume (RV) of >220% predicted, and pulmonary rehabilitation in the previous year.⁴ AATD was not an exclusion criterion. Patients randomized to the coil group received bilateral coil treatment in two sequential procedures. The most severely affected lobe of each lung was determined by each investigator using a visual score from 0 to 4. Coils were placed in the most affected lobe, with the upper lobe chosen when visual ipsilateral scores were the same. All patients had a 1-year follow-up, and patients in the usual care group were proposed ECT after the 1-year visit (cross-over group) with subsequent prespecified assessments at 6 and 12 months. AATD was defined by a PiZZ phenotype and a serum AAT level of less than 0.5 g/L.

In this post hoc analysis, we analyzed the safety and efficacy outcomes of all AATD patients who underwent ECT in the first phase or in the cross-over period, with end points at 6 months and 1 year after coil treatment.

The study was approved by the Ethics Committee of Dijon Est I (N°2012-A01477-36) and the French National Agency for Medicines and Health Products Safety (ANSM). Each patient signed a written informed consent.

Variables are presented as median [range] and percentages. Differences in efficacy and safety outcomes between AATD and non-AATD patients were analyzed using Wilcoxon tests for quantitative variables and Fisher's exact tests for qualitative variables, with no data imputation. A *P*-value <0.05 was considered as significant.

Case series

Among 100 patients included in the REVOLENS study, three AATD patients were randomized to the coil group and four AATD patients to the usual care group. One AATD patient randomized to the usual care group was not subjected to ECT after 1 year because of anticoagulation therapy for atrial fibrillation and active smoking. The remaining six AATD patients (five males, one female; mean age: 52±9 years) underwent bilateral ECT and were included in this post hoc analysis. Among these six patients, four received AAT augmentation therapy which was started before ECT. ECT was performed in the right upper lobe (n=3), left upper lobe (n=4), right lower lobe (n=3), and left lower lobe (n=2), with a median of 10 [8; 12] coils per lobe. Baseline, 6-month

changes, and 12-month changes in FEV₁, RV, 6MWT score, and quality of life assessed by the St George's Respiratory Questionnaire (SGRQ) are shown in Table 1. Significant improvement in hyperinflation defined by a minimal clinically important difference (MCID) of 0.35 L decrease in RV⁵ was observed in four out of six patients at 6 months and three out of six patients at 12 months. Significant improvement in quality of life defined by an MCID of 4 points in the SGRQ⁶ was observed in four out of six patients at both 6 and 12 months. One patient (case 4) exhibited a significant decrease in hyperinflation, whereas the quality of life did not improve. Of note, this patient had two serious adverse events (SAEs) and five non-SAEs within the 1-year follow-up, which included one pneumonia and four COPD exacerbations, which may explain the absence of response in terms of quality of life.

In an exploratory post hoc analysis, efficacy results at 6 and 12 months from the six AATD patients were compared with those from 84 non-AATD patients treated by coils in the REVOLENS study. This analysis suggested similar efficacy outcomes in AATD and non-AATD patients at 6 and 12 months with no difference in FEV₁, RV, 6MWT score, and SGRQ score (Table 2). SAEs and non-SAEs within 1 year in the six AATD patients who underwent ECT are shown in Table 1. Respiratory-related SAE was limited to pneumonia in one AATD patient. By comparison, SAEs within 1 year after ECT in the 84 non-AATD patients included deaths (five cases), pneumothorax (seven cases), COPD exacerbations (21 cases), pneumonia (16 cases), thoracic pain (four cases), hemoptysis (two cases) requiring hospitalization, and other causes (18 cases). When compared to non-AATD patients, the rates of SAEs and non-SAEs at 1 year in the six AATD patients were not statistically different (not shown).

Discussion

To our knowledge, this is the first study reporting efficacy and safety outcomes in AATD patients who underwent ECT. Our results suggest that ECT in AATD patients might be associated with a decrease in hyperinflation, an improvement in quality of life, and an acceptable safety profile at 1 year. However, our results must be interpreted with caution because of significant limitations. First, only six AATD patients were treated with coils in this study, leading to consider the present post hoc analysis as underpowered and exploratory, especially for comparisons with the non-AATD group. Second, only four out of six AATD patients received intravenous augmentation therapy. However, the impact of AAT augmentation therapy on our results should not be considered as a confounding factor because AAT augmentation

Table 1 Characteristics, coil treatment, changes at 6 and 12 months, and 1-year adverse events in AATD patients included in the REVOLENS study

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years), sex (M/F)	48, M	57, F	39, M	64, M	47, M	61, M
BMI (kg·m ⁻²)	23.7	20.3	27.8	24.1	25.1	21.8
Pack-years smoking	26	24	20	40	16	15
Augmentation therapy	No	Yes	No	Yes	Yes	Yes
Lobe, n coils						
First	RLL, 12	RLL, 10	RLL, 10	RUL, 12	RUL, 10	RUL, 10
Second	LLL, 10	LUL, 12	LLL, 11	LUL, 10	LUL, 10	LUL, 9
FEV ₁ , L (%)	0.68 (18)	0.82 (32)	1.22 (29)	0.62 (20)	0.96 (25)	0.81 (26)
Changes at 6 Mo, L	-0.05	+0.06	-0.25	+0.28	+0.08	-0.01
Changes at 12 Mo, L	-0.02	-0.13	-0.23	+0.26	-0.09	-0.07
RV, L (%)	6.51 (304)	5.44 (284)	5.68 (284)	7.29 (300)	6.2 (299)	5.94 (256)
Changes at 6 Mo, L	-0.42	+0.76	-0.5	-2.42	-0.04	-0.45
Changes at 12 Mo, L	-0.63	-0.32	+0.62	-1.09	-0.04	-0.47
6MWT, m	433	423	482	108	420	264
Changes at 6 Mo, m	-31	-3	+6	+102	0	-114
Changes at 12 Mo, m	-39	-13	+49	-48	0	-24
SGRQ, points	48	39	25	88	47	62
Changes at 6 Mo, L	-10	-2	-6	+1	-6	-9
Changes at 12 Mo, L	-10	-2	-6	+2	-5	-11
SAEs (in 1 year)	0	0	0	2	0	0
Pneumonia				1 ^a		
Other				1 ^b		
Non-SAEs (in 1 year)	3	6	0	5	12	3
COPD exacerbation	1	3	0	4	4	2
Pneumonia	0	0	0	0	2	0
Mild hemoptysis	0	0	0	0	2	1
Other respiratory	1	3	0	1	1	0
Non-respiratory	1	0	0	0	3	0

Notes: ^aPneumonia 6 days after the first coil treatment resolving with antibiotics and corticosteroids. ^bOne colonoscopy requiring hospitalization.

Abbreviations: AATD, alpha-1 antitrypsin deficiency; BMI, body mass index; F, female; LLL, left lower lobe; LUL, left upper lobe; M, male; Mo, months; RLL, right lower lobe; RUL, right upper lobe; RV, residual volume; SAEs, serious adverse events; SGRQ, St George's Respiratory Questionnaire.

therapy was started before ECT and maintained during the 1-year follow-up, and AAT augmentation therapy was not associated with significant changes at 1 year in FEV₁, RV, 6MWT score, and SGRQ score.⁷ Another limitation is the

lack of assessment by computed tomography scan of the lobar volume changes induced by ECT.

The present case series suggests that the positive effects of ECT in AATD patients are mainly represented by a

Table 2 Efficacy end points in AATD patients included in the REVOLENS study

Changes from baseline ^a	Alpha-1 antitrypsin patients (n=6)	Other patients (n=84)	P-value
6 months			
6MWT, m	-2 [-114; +102]	+1 [-224; +205]	0.60 ^b
FEV ₁ , L	+0.03 [-0.25; +0.28]	+0.03 [-0.28; +0.59]	0.87 ^b
RV, L	-0.44 [-2.42; +0.76]	-0.39 [-2.51; +1.41]	0.89 ^b
SGRQ total	-6 [-10; +1]	-8 [-47; +35]	0.59 ^b
12 months			
6MWT, m	-19 [-48; +49]	0 [-200; +188]	0.57 ^b
FEV ₁ , L	-0.08 [-0.23; +0.26]	+0.02 [-0.37; +0.59]	0.10 ^b
RV, L	-0.40 [-1.09; +0.62]	-0.41 [-2.77; +2.45]	0.85 ^b
SGRQ total	-6 [-11; +2]	-5 [-47; +32]	0.99 ^b

Notes: ^aData are expressed as median [range]. ^bWilcoxon test.

Abbreviations: AATD, alpha-1 antitrypsin deficiency; RV, residual volume; SGRQ, St George's Respiratory Questionnaire.

decrease in hyperinflation and an improvement in quality of life, whereas changes in FEV₁ and 6MWT score are mild and do not reach the MCID for most of the AATD patients. The other important point to consider is that only one respiratory-related SAE occurred within 1 year after ECT in one of the six AATD patients, suggesting the safety of ECT in AATD patients. Because of the significant limitations of this post hoc analysis, additional studies are clearly needed to determine the efficacy and safety of ECT in AATD patients. So far, available data regarding the safety and efficacy of ELVR in AATD are limited to endobronchial valves with one retrospective monocentric study including 15 consecutive AATD patients among which 12 patients were assessed at 1 year⁸ and one prospective study including six AATD patients with a mean duration of follow-up of 8 months,⁹ both showing significant improvements in FEV₁.

In conclusion, this post hoc analysis of the REVOLENS study suggests that AATD patients with severe emphysema may have similar efficacy and safety outcomes at 1 year after ECT as non-AATD-related emphysema. Because of the paucity of available data, these results advocate for conducting appropriately powered studies to assess the effects of ECT in AATD.

Data and safety management board

The data and safety management board members include François Fourrier MD PhD, Eric Hachulla MD PhD, Nicolas Roche MD PhD, and Daniel Dusser MD PhD. These collaborators did not receive any compensation for their contribution.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. Gaëtan Deslee had full access to all of the data in the study and takes responsibility for the integrity of data and accuracy of data analysis. Study concept and design was developed by Jeanne Marie Perotin, Gaëtan Deslee, Charles Hugo Marquette, and Coralie Barbe. Data acquisition was performed by Jeanne Marie Perotin, Gaëtan Deslee, Sylvie Leroy, Hervé Mal, Hervé Dutau, Arnaud Bourdin, Jean Michel Vergnon, Christophe Pison, and Charles Hugo Marquette. Data analysis and interpretation were carried out by Jeanne Marie Perotin, Gaëtan Deslee, Charles Hugo Marquette, and Coralie Barbe. Manuscript was drafted by Jeanne Marie Perotin, Sylvie Leroy, Charles Hugo Marquette, and Gaëtan Deslee. Critical revision of the manuscript for important intellectual content was done by Jeanne Marie Perotin, Sylvie Leroy, Charles Hugo Marquette, Hervé Mal, Hervé

Dutau, Arnaud Bourdin, Jean Michel Vergnon, Christophe Pison, Coralie Barbe, and Gaëtan Deslee. Statistical analysis was carried out by Coralie Barbe. The study was supervised by Gaëtan Deslee.

Disclosure

Gaëtan Deslee has been involved as an investigator in previous studies sponsored by BTG/PneumRx, and received travel reimbursements and speaker fees for educational sessions and consulting from BTG/PneumRx. Hervé Mal received honorarium from Boehringer, Bayer, Roche, Astellas, Chiesi, Actellion, Pfizer, Novartis, and GlaxoSmithKline outside the submitted work. Hervé Dutau received travel reimbursements and speaker fees for educational sessions and consulting from BTG/PneumRx. Arnaud Bourdin received honorarium from Astra Zeneca, GlaxoSmithKline, Boehringer, Novartis, Teva, Chiesi, Actellion, Gilead, and Roche outside the submitted work. Jean Michel Vergnon received travel reimbursements and speaker fees for educational sessions from BTG/PneumRx. Christophe Pison received honorarium from BTG/PneumRx and his hospital received funds to conduct trials from Holaira, PulmonX, and BTG/PneumRx. Charles Hugo Marquette has been involved as an investigator in previous studies sponsored by BTG/

PneumRx, and received travel reimbursements and speaker fees for educational sessions and consulting from BTG/PneumRx. The authors report no other conflicts of interest in this work.

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