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Bronchoscopic Lung Volume Reduction in Patients with Emphysema due to Alpha-1 Antitrypsin Deficiency

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Keywords
Bronchoscopic lung volume reduction · Emphysema · Alpha-1 antitrypsin deficiency · COPD

Abstract
Background: Bronchoscopic lung volume reduction using one-way endobronchial valves (EBVs) is a valid therapy for severe emphysema patients. However, alpha-1 antitrypsin (AAT)-deficient patients were excluded from the majority of clinical trials investigating this intervention. ***Objectives:*** The aim of this study was to investigate the feasibility, efficacy, and safety of EBV treatment in patients with AAT deficiency (AATD) or a reduced AAT level. ***Method:*** A retrospective analysis was performed of all patients treated with EBV with confirmed AATD or with a reduced AAT serum level at the University Medical Center Groningen between 2013 and 2021. Baseline and 6-month follow-up assessment included chest CT, pulmonary function measurement, 6-min walking distance (6MWD), and St. George's Respiratory Questionnaire (SGRQ). ***Results:*** In total, 53 patients were included, 30 patients in the AATD group (AAT <0.6 g/L or confirmed ZZ phenotype) and 23 patients in the reduced AAT group (AAT 0.6–1 g/L). In both groups, all response variables improved significantly after treatment. There was a median increase in forced expiratory volume in 1 s of 105 mL (12% relative) and 280 mL (31% relative) in the AATD and reduced AAT groups, respectively. 6MWD increased by 62 min and 52 min, and SGRQ decreased by 12.5 patients and 18.7 patients, respectively. A pneumothorax occurred in 10% and 13% of patients, and no patients died. ***Conclusions:*** EBV treatment in patients with emphysema and AATD or a reduced AAT level is feasible and results in significant improvements in pulmonary function, exercise capacity, and quality of life and has an acceptable safety profile.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a rare, genetic cause for the development of COPD. Alpha-1 antitrypsin (AAT) is a serum protease mainly produced by liver hepatocytes. A number of mutations in the SERPINA1 gene on chromosome 14 cause a variety of AATD phenotypes. The prevalence of a mutation in this gene is about 10%, but severe AATD is rare, estimated at 1:2,000 to 1:3,000, depending on the geographic region. The most common cause of severe AATD is Z allele homozygosity, whereas heterozygous variants are generally less severe [1]. In the lung, an imbalance in protease/antiprotease activity predisposes to proteolytic tissue damage, next to

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local polymer formation, further inducing local inflammation [2]. These effects are enhanced by inflammation caused by cigarette smoking. Most patients with severe AATD become symptomatic as early as from the third decade of life, in contrast to regular COPD patients, mostly diagnosed after their fifth decade. Emphysema in AATD typically presents as panlobular and predominantly in the lower lobes, in contrast to the centrilobular and apical smoking-induced emphysema. However, similar to "usual" COPD, AATD has a heterogeneous clinical and radiological presentation [1].

Standard treatment of patients with COPD due to AATD is similar to treatment of COPD patients with replete AAT, among others like smoking cessation, optimal medical therapy, pulmonary rehabilitation, and in a minority of cases, lung transplantation. In some patients, intravenous administration of AAT from pooled human plasma is a specific treatment able to reduce the decline in lung density on CT scans. However, the lack of effect on forced expiratory volume in 1 s (FEV_1), diffusion capacity for carbon monoxide (DL_{CO}), and quality of life, after 2 years of follow-up, is the reason that this treatment is not reimbursed in many countries [3].

In the last decade, bronchoscopic lung volume reduction (BLVR) using one-way endobronchial valves (EBVs) became an effective treatment for COPD patients with advanced emphysema, hyperinflation, and the absence of interlobar collateral ventilation. The rationale is to reduce hyperinflation, which leads to a significant improvement in dynamic lung volumes, exercise capacity, and quality of life [4–6]. In approvals of EBV, no distinction has been made between patients with or without AATD. However, AATD patients were excluded from the majority of clinical trials investigating this therapy because of the distinct emphysema phenotype and due to poor historical results of lung volume reduction surgery (LVRS) in AATD and of treatment of the lower lobes in general [7–9]. Only small case series about EBVs in AATD have been published to date, showing promising results [10–12]. Therefore, we hypothesized that patients with AATD-related emphysema can be treated successfully by BLVR using EBVs and set out to retrospectively analyze the results of EBV treatment in this specific patient group.

Materials and Methods

Study Design

This is a single-center retrospective study on emphysema patients with AATD treated with BLVR by EBVs between 2013 and 2021 at the University Medical Center Groningen, the Netherlands. Patients were included from the BREATHE-NL registry (NCT02815683), the STELVIO trial (NTR2876) [4], TRANSFORM trial (NCT02022683) [5], or were treated under compassionate use. Only patients with known AATD and a reduced serum AAT level or a confirmed phenotype and a 6-month follow-up visit were included in the analysis. All patients signed written informed consent for use of their data.

Two groups were formed based on the serum AAT level. One group comprised patients with serum levels below 0.6 g/L or a confirmed ZZ phenotype (AATD group). The other group comprised patients with possible or mild AATD based on reduced serum AAT levels between 0.6 and 1 g/L (reduced AAT group) [13].

Measurements

Both at baseline and at follow-up, pulmonary function, high-resolution chest CT scan (HRCT) and quantitative CT analysis (LungQ, Thirona, Nijmegen, The Netherlands), 6-min walking distance (6MWD), and the St. George's Respiratory Questionnaire (SGRQ) [14] were obtained. A follow-up CT scan was performed at 6 weeks. Other follow-up data were obtained at 6 months. If no 6-month follow-up data were available, the next follow-up measurement was used. Heterogeneous emphysema was defined as a difference ≥15% in voxels below −950 HU between the target lobe and the ipsilateral lobe on HRCT. Lung function variables were measured by post-bronchodilator spirometry, body plethysmography, and DL_{CO} using the Jaeger MasterScreen™ (CareFusion, Germany), according to ATS/ERS guidelines [15–17]. Reference values from the European Community for Coal and Steel were used [18]. The 6-min walking test was performed in accordance with ATS recommendations [19].

Endobronchial Lung Volume Reduction

Patients underwent the EBV treatment under general anesthesia. The target lobe was selected based on quantitative CT analysis as described before [20]. Chartis measurement (Chartis®, Pulmonx Corporation, Redwood City, CA, USA) was performed in all patients to investigate the presence of collateral ventilation between the ipsilateral lobes, as described before [21]. In case of the absence of collateral ventilation, EBVs (Zephyr® EBV, Pulmonx Corporation, Redwood City, CA, USA) were placed in all (sub) segments of the treatment target lobe in order to induce a desired atelectasis.

Statistical Analyses

Baseline characteristics were compared between two groups with Mann-Whitney U and χ^2 tests for continuous variables and frequencies, respectively. To evaluate response in FEV_1, RV, TLC, RV/TLC, 6MWD, and SGRQ at 6 months, a Wilcoxon signed rank test was performed (both absolute and relative change). Response rates based on the minimal clinically important difference (MCID) were calculated and presented as percentages. The MCID cutoffs used were relative increase in FEV_1 ≥12%, a decrease in RV ≥430 mL, an increase in 6MWD ≥26 m, a decrease of SGRQ total score of 7 points, and a target lobe volume reduction (TLVR) of 563 mL [22–27]. SPSS (IBM SPSS Statistics 23, Armonk, NY, USA) was used for analyses. $p < 0.05$ was considered significant.

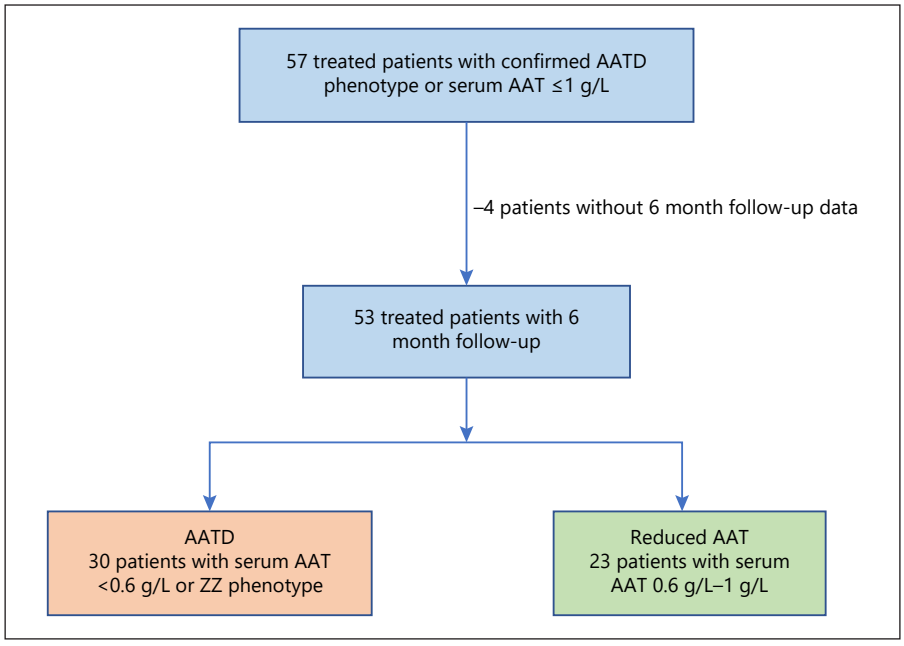

Fig. 1. Flowchart of which patients were included in the analysis and how two groups were formed. AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin.

Table 1. Baseline characteristics

	AATD	Reduced AAT	*p* value
Number	30	23	
Female (%)	20 (67)	17 (74)	0.569
Age, years	55 (46–62)	64 (59–68)	0.002
BMI, kg/m^2	24 (21–26)	25 (21–26)	0.986
Pack-years, years	14 (8–21)	36 (26–45)	<0.001
AAT serum, g/L	0.2 (0.2–0.3) (*n* = 19)	0.9 (0.8–1.0)	<0.001
Genotype ZZ/MZ/unknown (%)	20 (67)/1 (3)/9 (30)	–/2 (9)/21 (91)	NA
FEV_1, %	30 (25–35)	27 (24–35)	0.095
FVC, %	78 (69–87)	81 (65–94)	0.858
RV, %	222 (199–280)	234 (211–258)	0.542
TLC, %	134 (126–143)	137 (131–148)	0.501
RV/TLC	60 (55–66)	64 (60–70)	0.043
DL_{CO}, %	35 (31–44) (*n* = 26)	34 (28–43) (*n* = 22)	0.444
6MWD, m	355 (265–424) (*n* = 29)	338 (282–415)	0.934
SGRQ, points	55.4 (43.8–62.3) (*n* = 28)	56.0 (44.7–65.7) (*n* = 22)	0.769
mMRC	2 (2–3)	3 (2–3)	0.234
Heterogeneous emphysema (%)	26 (87)	23 (100)	0.069
Target lobe volume, mL	1,744 (1,369–2,275)	1,883 (1,548–2,150)	0.370
Target lobe voxels <–950 HU, %	54 (47–58)	50 (43–54)	0.146

AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DL_{CO}, diffusion capacity for carbon monoxide; 6MWD, 6-min walking distance; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council dyspnea scale; NA, not applicable.

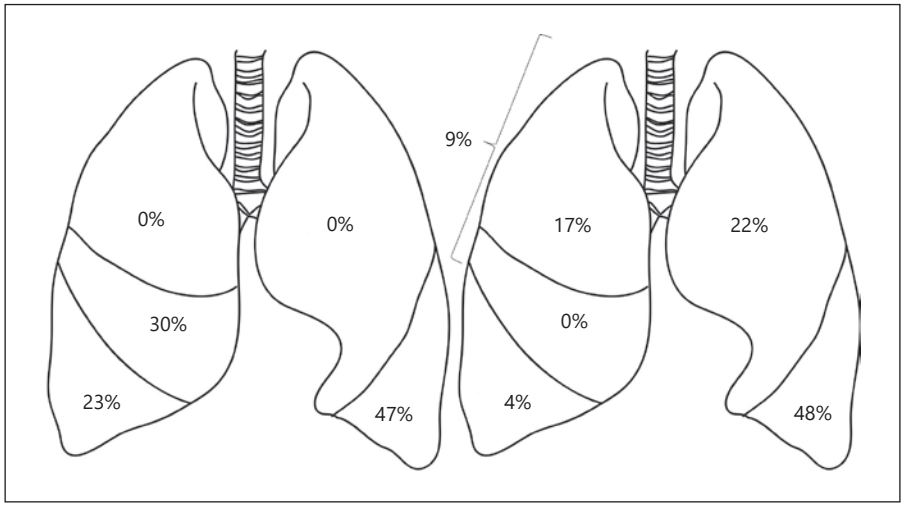

Fig. 2. Difference in target lobes between the groups. Left illustration represents the AATD group and right illustration represents the reduced AAT group, $p < 0.001$. AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin.

Results

Dataset and Baseline Characteristics

From the screened datasets, 57 treated patients were found to have AATD or a reduced AAT serum level. Of these patients, 4 were excluded due to missing 6-month follow-up data. Reasons were diagnosis and treatment of breast carcinoma (1), extraction of EBVs because of recurrent pneumothorax (1) or lack of effect (1), and death by contralateral pneumothorax (1). Therefore, in total, 53 patients were included in this analysis (30 patients in the AATD group and 23 patients in the reduced AAT group based on serum AAT levels and confirmed phenotype [shown in Fig. 1]). Baseline characteristics are shown in Table 1.

In the AATD group, the median AAT serum level was 0.2 (IQR 0.2–0.3) g/L versus 0.9 (0.8–1.0) g/L in the reduced AAT group. The ZZ phenotype was confirmed in 20 (67%) patients, MZ in 1 patient (3%), and the mutation was unknown in 9 patients (30%) (shown in Table 1). The AATD patients were significantly younger (55 [46–62] versus 64 [59–68] years, $p < 0.01$) and smoked less (14 [8–21] versus 36 [26–45] pack-years, $p < 0.001$). There was no significant difference in FEV_1, RV, or DL_{CO}, but a less pronounced hyperinflation, based on a significant lower RV/TLC ratio, was present in the AATD group (60 [55–66] versus 64 [60–70], $p < 0.05$). No significant difference in baseline 6MWD and SGRQ was present between groups.

Heterogeneous emphysema distribution was present in 87% patients of the AATD group and 100% in the reduced AAT group (not significant between groups). In the AATD group, only the right middle lobe (RML) (30%) and lower lobes (70%) were treated, whereas upper lobes were treated in 11 out of 23 (48%) patients of the reduced AAT group (shown in Fig. 2) ($p < 0.001$). The median target lobe volume and destruction scores were comparable between groups.

Treatment Response

A TLVR larger than the MCID of 563 mL was achieved on 6-week follow-up HRCT in 27/30 (90%) patients in the AATD group and in 22/23 (96%) of patients in the reduced AAT group (shown in Fig. 3a). Median time to follow-up measurements was equal in both groups (182 and 181 days). All response variables were significantly improved at follow-up compared to baseline in both groups. There was a median increase in FEV_1 of 105 mL or 12% relative and 280 mL or 31% relative in the AATD and reduced AAT groups, respectively. RV improved by −465 mL (9% relative) and −980 mL (−20% relative), 6MWD increased by 62 m and 52 m, and SGRQ improved by −12.5 points and −18.7 points in AATD and reduced AAT groups, respectively (Table 2). The proportions of patients reaching the MCID for all variables are shown in Figure 3, with a 50–80% response rate for the different variables.

Safety

A pneumothorax occurred in 3 patients (10%) of the AATD group and in 3 patients (13%) of the reduced AAT group. Revision bronchoscopy within 6 months was performed in 3 (10%) and 2 (9%) patients in AATD and reduced AAT groups, respectively. In all 5 patients, revision was performed because of lack of effect, and at least one valve was replaced.

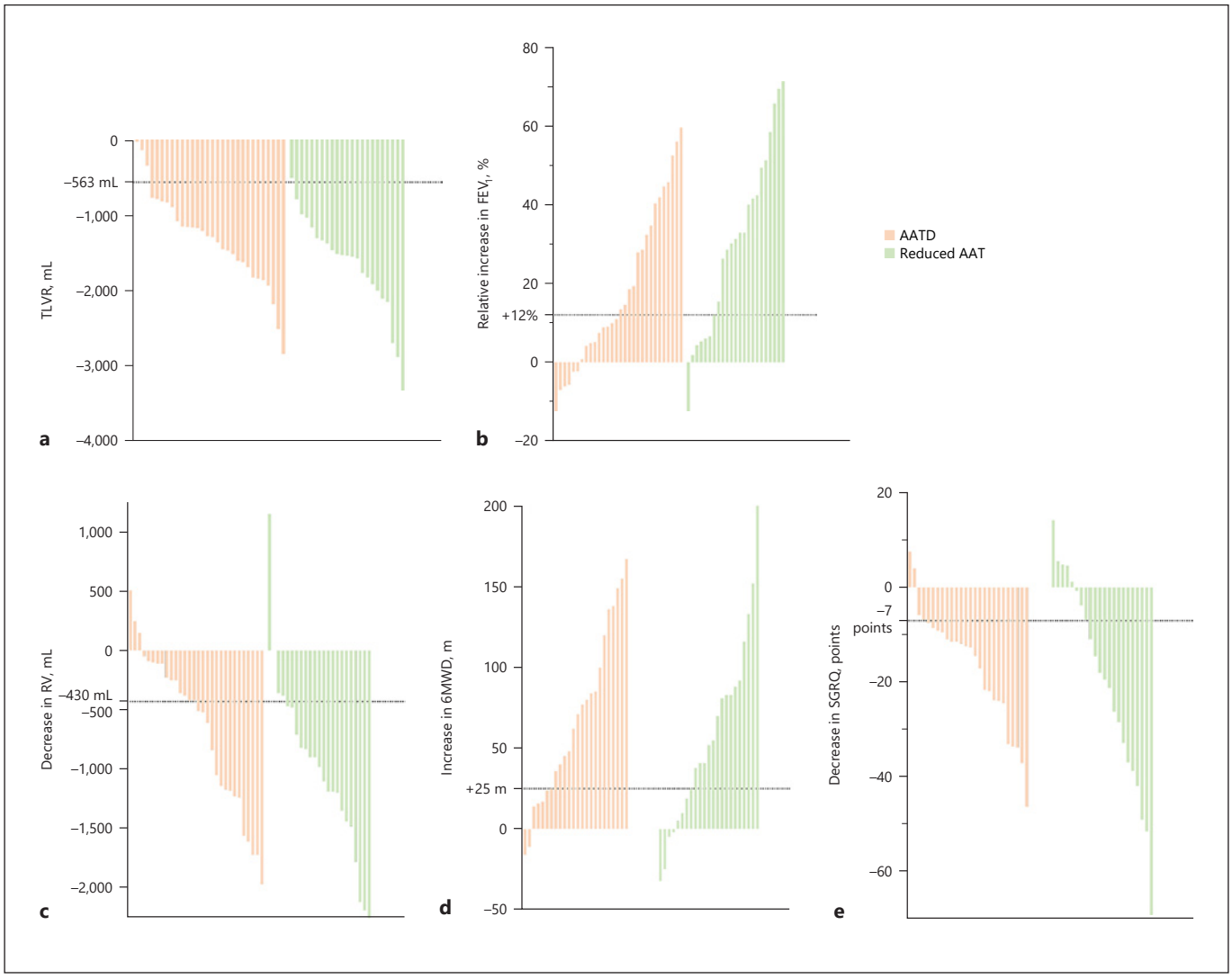

Fig. 3. Response rates based on minimal clinical important difference (MCID) in both AATD and reduced AAT groups. Every bar represents an individual patient. Dashed lines represent the MCID cutoff (TLVR of ≥563 mL, increase in FEV_1 ≥12%, decrease in RV ≥430 mL, increase in 6MWD ≥26 m, decrease of SGRQ >7 points). In panel **a**, target lobe volume reduction (TLVR), in panel **b**, relative increase of forced expiratory volume in 1 s (FEV_1), in panel **c**, decrease in residual volume (RV), in panel **d**, increase in 6-min walking distance (6MWD), and in panel **e**, decrease in points in the St. George's Respiratory Questionnaire (SGRQ). AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin.

Discussion

This study demonstrates that the EBV treatment is a feasible, effective, and a safe treatment option in selected patients with AATD and patients with suspicion of mild AATD based on reduced serum levels. Although these patients are often young and severely impaired by emphysema, they were excluded in most of the randomized clinical trials investigating EBV treatment. Therefore, these patients are often not considered for EBV treatment by their treating physicians despite the fact that they are good candidates for this treatment.

Previous case series on endobronchial LVR in AATD studied a smaller and different population. Irish authors reported a case series of 6 patients who were referred for lung transplantation with very severe disease (median baseline FEV_1 of 18.3%). Median improvement in FEV_1 was +265 mL at 8-month follow-up [10]. Hillerdal et al. [11] reported on 15 AATD patients, with a baseline mean FEV_1 of 25%, of which 2 had undergone a single lung

Table 2. Changes in clinical outcomes between baseline and 6-month follow-up in AATD and reduced AAT groups

	AATD	Reduced AAT
Number	30	23
Time to follow-up, days	182 (169–206)	181 (168–196)
ΔFEV_1, mL	+105 (40–330)	+280 (50–400)
% increase in FEV_1	+12 (3–36)	+31 (7–49)
ΔRV, mL	−465 (1,193–110)	−980 (1,440–480)
% decrease in RV	−9 (26–3)	−20 (31–14)
ΔRV/TLC	−4 (2–14)	−8 (5–16)
Δ6MWD, m	+62 (25–110) (n = 25)	+52 (10–88)
ΔSGRQ, points	−12.5 (9.0–24.0) (n = 26)	−18.7 (0.2–37.3) (n = 22)

Results are presented as median (interquartile range). AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin; FEV_1, forced expiratory volume in 1 s; RV, residual volume; TLC, total lung capacity; 6MWD, 6-min walking distance; SGRQ, St. George's Respiratory Questionnaire. Difference compared to baseline was analyzed with the Wilcoxon signed rank test. All outcomes were significantly different between baseline and 6-month follow-up in both AATD and reduced AAT groups, all $p < 0.01$.

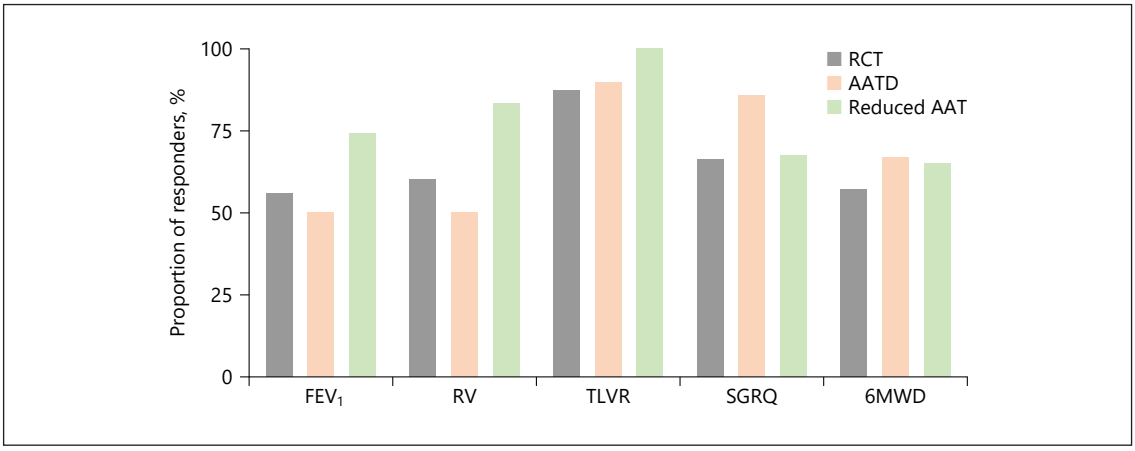

Fig. 4. Proportion of responders in AATD and reduced AAT groups next to the mean responder rate from 4 RCTs on endobronchial lung volume reduction. As minimal important clinical difference (MCID), the following cutoffs were used: increase in FEV_1 ≥12% (≥10% in the STELVIO trial), decrease in RV ≥430 mL (310 mL in the LIBERATE trial), TLVR of ≥350 mL, increase in 6-min walking distance (6MWD) ≥26 m, and decrease in points in the St. George's Respiratory Questionnaire (SGRQ) of ≥4 points. AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin; RCT, randomized controlled trials; FEV_1, forced expiratory volume in 1 s; RV, residual volume; TLVR, target lobe volume reduction; 6MWD, 6-min walking distance; SGRQ, St. George's Respiratory Questionnaire.

transplantation before. At 6 months, a mean FEV_1 increase of 38% was reported; no other outcomes were analyzed. These results on FEV_1 seem larger than the ones of the present study, but the baseline FEV_1 was much lower. The smallest case series also reported on 6MWD and SGRQ, and the results are in line with our study (median increase +71 m on 6MWD and median improvement of −10.9 points on SGRQ) [10]. A more recent conference abstract showed data on EBVs in 20 AATD patients with mean baseline FEV_1 of 0.87 L and mean 0.11 L improvement at 6 months and 0.07 L at 12 months. Mean improvements in 6MWD and SGRQ were above MCID [12].

Compared to the current literature, the present study investigated a larger group of AATD patients, varying from patients with mildly reduced AAT levels to severely deficient patients. Severe AATD is clearly a distinct COPD phenotype, which is also confirmed by the base-

line characteristics of our groups showing significant difference in age and smoked pack-years. The reduced AAT group resembles a regular COPD population. There has been controversy on emphysema risk in patients with mild reduction of AAT levels. However, in a recent study, the heterozygous MZ phenotype was compared to COPD patients without mutation (MM), and a significant difference in lung function and emphysema was found. As a consequence, MZ was considered a distinct endotype [28]. These findings demonstrate that also mildly reduced AAT levels could be of pathophysiological and clinical relevance.

The perceived difference in lung functional response rate between AATD patients and patients with reduced AAT, despite high response on TLVR in both groups, may be explained by more pronounced hyperinflation at baseline and significant difference in the location of the target lobe in the reduced AAT group, where more upper lobes were treated. Although the difference between baseline target lobe volumes was not significant, the fact that 30% of patients in the AATD group were treated in the RML, which is generally the smallest lobe, may also explain less pronounced lung functional response in this group. Figure 4 shows the response rates of both groups compared to previous randomized controlled trials, in which AATD was an exclusion criterion or a minority. Results on SGRQ and 6MWD in the AATD group were at least as good as results of previous randomized controlled trials.

It is striking that the RML was the target of treatment in 9 AATD patients (30%) versus zero patients in the reduced AAT group. In the latter, the right upper lobe (RUL) was treated together with RML in 2 patients (9%). The treated RMLs were the primary target in these patients based on combination of destruction score and lobar volume. In previously published data on endobronchial LVR in AATD, RML was also target of treatment in 2/6 (33%) and 2/15 (13%) patients [10, 11]. The pathophysiology of emphysema and hyperinflation specifically in the RML of AATD patients is, to our knowledge, not investigated nor understood. In contrast, one report on CT appearance of emphysema in AATD versus regular COPD described higher emphysema scores in the RML of patients with regular COPD compared to AATD patients. However, the sample size was very small (n = 14), and there were no differences in age and pack-years between groups, which questions the investigated AATD phenotype [29]. In contrast to LIBERATE and IMPACT, AATD was not an exclusion criteria in the TRANSFORM study, although the manuscript does not mention prevalence of AATD in the treated patients group. In these studies, the RML was never treated as a single target. The combination of RUL and RML treatment was performed in 5/65 patients (7.7%) in the TRANSFORM study and in 8/128 patients (6.3%) in the LIBERATE study. In the IMPACT study, in which homogeneous emphysema was treated, treatment of RML was not allowed [30]. [5, 6, 30]. The 7 AATD patients, who were treated in the STELVIO trial, were all included in our analysis. Of these, 1 had the RML and 1 had both the RML and RUL treated. No other patients were treated in the RML, whereas 10 more patients were treated in both RML and RUL [4]. More research on emphysema pathophysiology in AATD is needed to understand the mechanism of RML destruction. If the RML is the primary target, LVR by use of one or two valves is a relatively uncomplicated and elegant option [31].

Other lung volume-reducing strategies in AATD have been poorly investigated. A post hoc analysis of the REVOLENS study reports on endobronchial coil treatment of 6 patients with AATD. Results on FEV_1, RV, 6MWD, and SGRQ at 1 year were comparable with non-AATD patients [32]. In general, coil treatment has less pronounced effect on hyperinflation, and if patients fulfill criteria, treatment with EBVs is preferable. With regards to surgery, the often basal location of emphysema in AATD is technically more challenging and studies showed less preserved effects after surgery and even higher mortality compared to AAT-replete patients [33]. This is the reason why LVRS is currently not recommended in AATD patients. However, these studies were small, and the current less-invasive surgical techniques in combination with early recovery protocols may improve results. New studies on LVRS in AATD should provide further guidance.

The retrospective design of this study is a limitation. The AAT mutation was not known in many patients, especially in the patients with a reduced AAT level, between 0.6 g/L and 1 g/L, where we suspect mild AATD without having it confirmed genetically. C-reactive protein level, age, oral contraception, hypoproteinemia, and liver function, all of which are known to influence AAT levels, were not considered while interpreting the AAT serum level. We reported on the 6-month outcome, which allows only short-term evaluation of treatment effect. Whether BLVR has less long-lasting effect in AATD patients compared to regular lung emphysema, such as assumed for surgical LVR, is not known and should be investigated in future studies. Of course, this treatment option is only for a selected group of AATD patients, and criteria and recommendations for endobronchial lung volume reduction

should be fulfilled to obtain good results [20]. However, successful treatment of AATD patients is very relevant since no other lung function improving therapies are available at this moment, and lung transplantation is preferably postponed until the sixth decade of age. Burden of this disease for patients, caregivers, and healthcare systems has recently been shown, and the latter seems higher compared to non-AATD COPD patients [34].

The results of the present study support BLVR using EBVs in patients with both mild and severe AATD. The functional outcome and quality of life were encouraging at 6 months and without safety concerns. If patients with AATD and significant lung emphysema suffer from hyperinflation, assessment for treatment with EBVs for lung volume reduction should be considered.

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Statement of Ethics

All included patients supplied written informed consent, and the studies in which they participated were all approved by the local Ethics Committee of the University Medical Center Groningen (METc 2016.483, METc 2011.095, METc 2016.022).

Conflict of Interest Statement

Stephanie Everaerts received lecture fees from Boehringer Ingelheim, GSK, and AstraZeneca; registration fees and travel costs from Chiesi, GSK, and Sanofi; and participation in advisory boards of GSK and Chiesi; none regarding the presented study. Jorine Hartman, Marlies Van Dijk, and David Koster do not report any conflicts of interest. Dirk-Jan Slebos reported grants or contracts, registration fees, and travel costs and participation on the DSMB from PulmonX, Corp. and BTG/PneumRx Inc., outside the current study. Karin Klooster has reported lecture fees from PulmonX and Chiesi pharmaceuticals B.V., outside of the current study.

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Author Contributions

Stephanie Everaerts, Jorine Hartman, Dirk-Jan Slebos, and Karin Klooster contributed to the study concept and design. Marlies Van Dijk, David Koster, and Dirk-Jan Slebos performed procedures. Stephanie Everaerts, Jorine Hartman, and Karin Klooster performed data collection. Stephanie Everaerts performed statistical analysis and wrote the manuscript. All the authors critically reviewed the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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