



Improved treatment response to dornase alfa in cystic fibrosis patients using controlled inhalation

E.M. Bakker*, S. Volpi[#], E. Salonini[#], E.C. van der Wiel-Kooij*,
C.J.J.C.M. Sintnicolaas[†], W.C.J. Hop⁺, B.M. Assael[#],
P.J.F.M. Merkus[†] and H.A.W.M. Tiddens*

ABSTRACT: Better treatment of obstructed small airways is needed in cystic fibrosis. This study investigated whether efficient deposition of dornase alfa in the small airways improves small airway obstruction.

In a multicentre, double-blind, randomised controlled clinical trial, cystic fibrosis patients on maintenance treatment with 2.5 mL dornase alfa once daily were switched to a smart nebuliser and randomised to small airway deposition (n=24) or large airway deposition (n=25) for 4 weeks. The primary outcome parameter was forced expiratory flow at 75% of forced vital capacity (FEF_{75%}).

FEF_{75%} increased significantly by 0.7 sd (5.2% predicted) in the large airways group and 1.2 sd (8.8% pred) in the small airways group. Intention-to-treat analysis did not show a significant difference in treatment effect between groups. Per-protocol analysis, excluding patients not completing the trial or with adherence <70%, showed a trend (p=0.06) in FEF_{75%} Z-score and a significant difference (p=0.04) between groups in absolute FEF_{75%} (L·s⁻¹) favouring small airway deposition.

Improved delivery of dornase alfa using a smart nebuliser that aids patients in correct inhalation technique resulted in significant improvement of FEF_{75%} in children with stable cystic fibrosis. Adherent children showed a larger treatment response for small airway deposition.

KEYWORDS: Aerosol deposition, inhaled drug delivery, nebuliser, paediatric, small airways

Cystic fibrosis (CF) lung disease is characterised by chronic airway infection and inflammation that start early in life and cause progressive structural lung damage, which eventually leads to respiratory failure and early death [1–3]. Small airways are involved early in the disease process [4], as indicated by trapped air on CT scans [5, 6] and by lung function tests [7, 8] of young children.

Sputum of CF patients is rich in leukocyte-derived DNA that contributes to its abnormal viscoelasticity, which in turn leads to small airway obstruction [9]. A major challenge in the treatment of CF is, therefore, to mobilise as much sputum as possible from the airways. Airway clearance techniques and nebulisation of mucolytic drugs play an important role in mobilising sputum.

Recombinant human DNase (dornase alfa) is a mucolytic drug that has been extensively investigated in CF and is part of current standard

treatment. Dornase alfa cleaves extracellular DNA through hydrolysis and reduces the viscoelasticity of CF sputum *in vitro* [10]. Dornase alfa has been shown to improve lung function and reduce the number of pulmonary exacerbations in CF patients [11–13]. In a study in children with normal forced vital capacity (FVC), a treatment benefit of 7.9% predicted was observed for the forced expiratory flow between 25% and 75% of FVC (FEF_{25–75%}), compared with a benefit of only 3.2% pred in the primary outcome parameter, forced expiratory volume in 1 s (FEV₁) [13]. FEF_{25–75%} and forced expiratory flow at 75% of FVC (FEF_{75%}) are considered sensitive to changes in the small airways [14].

Because most CF patients show lung function evidence of persistent small airway obstruction [13, 15] and patients with advanced lung disease have extensive destruction of the small airways [16, 17], more efficient treatment of the small airways is still needed [18]. This could be achieved

AFFILIATIONS

*Dept of Paediatric Pulmonology and Allergology, Erasmus MC – Sophia Children's Hospital,

[†]Dept of Biostatistics, Erasmus MC, Rotterdam,

[‡]Dept of Paediatric Pulmonology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

[#]Cystic Fibrosis Center, Verona, Italy.

CORRESPONDENCE

H.A.W.M. Tiddens

Erasmus MC – Sophia Children's Hospital
Room Sp-3570
PO Box 2060
3000 CB Rotterdam
The Netherlands
E-mail: h.tiddens@erasmusmc.nl

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through improved delivery of dornase alfa to the small airways. Currently, dornase alfa is routinely administered with relatively inefficient nebulisers. These nebulisers deposit most of the inhaled drug in large airways and relatively little of the drug in the small airways [19, 20]. This is primarily due to two nebuliser-related factors: particle size of the inhaled aerosol and breathing pattern during inhalation. Standard jet nebulisers produce an aerosol with a wide range of particle sizes and a relatively large mean particle size. Large aerosol particles have a high probability to get deposited in the central airways. Furthermore, most patients perform tidal breathing while using a standard nebuliser. This leads to preferential deposition of particles in the large airways. In contrast, a slow and deep inhalation increases the probability of particle deposition in the small airways.

Recently, smart nebulisers have become available that coach patients in proper inhalation technique, are more efficient in drug delivery and can target more of the inhaled dose to the small airways [21–23]. However, it is unknown whether preferential delivery of dornase alfa to small airways using a state-of-the-art nebuliser actually improves small airway patency in children with CF. To answer this question, we conducted a randomised controlled clinical trial comparing large and small airway deposition of dornase alfa in stable CF patients using a state-of-the-art nebuliser.

METHODS

We conducted a multicentre, double-blind, randomised controlled clinical trial in stable paediatric CF patients who were on maintenance treatment with 2.5 mg dornase alfa once daily, to compare the efficacy of small airway *versus* large airway deposition of dornase alfa using a breath-controlled nebuliser.

Patient recruitment and randomisation

Study participants were recruited from the outpatient clinics of three participating hospitals: Erasmus MC – Sophia Children's Hospital (Rotterdam, the Netherlands), Radboud University Nijmegen Medical Centre (Nijmegen, the Netherlands) and the Cystic Fibrosis Center (Verona, Italy).

CF patients were eligible to participate in the study if they were aged 6–18 yrs, in stable condition, on maintenance treatment with 2.5 mg dornase alfa once daily and had small airway obstruction present on spirometry (defined as FEF_{75%} <70% pred). A full checklist of inclusion, exclusion and study stop criteria used in the study is available in the online supplementary material.

Patients were randomly assigned to the small airway deposition group or the large airway deposition group, according to the randomisation schedule prepared by the study statistician. The hospital pharmacy was responsible for the administration of randomisation data and guaranteed 24-h availability of randomisation information.

This trial was registered in the Dutch trial register (www.trialregister.nl) and in the International Standard Randomised Controlled Trial Number Register (number 64225851). The local ethics committee approved the study. Parental written informed consent and children's assent were obtained prior to the first study measurement.

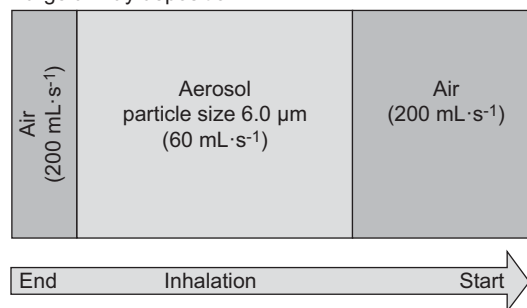
Study treatment

Study treatment consisted of targeted peripheral or central deposition of 2.5 mg (2.5 mL) dornase alfa. Central deposition simulated conventional nebulisers and deposited most of the drug in the large airways (large airways group), while peripheral deposition optimised deposition in the small airways (small airways group) [21, 24–26]. Dornase alfa was inhaled once daily using the Akita² APIXNEB device (Activaero Technologies, Gemünden, Germany). This device consists of a nebuliser handset (APIXNEB) that uses vibrating mesh technology (Touchspray; PARI GmbH, Starnberg, Germany) and an electronic unit (Akita²). In this publication, we will refer to this device as Akita². The Akita² deposits ~70% of the loaded dose in the lung [26], compared with 10–20% for conventional jet nebuliser systems [27–30]. Therefore, total lung dose of dornase alfa during this study was estimated to be 3–5 times higher than with standard jet nebulisers. The Akita² can be programmed to preferentially target specific regions of the lung [21, 24–26]. The Akita² directs the flow and depth of each inhalation, coaches the patient on correct inhalation technique and controls the fraction of the inspiration time during which aerosol is generated. These settings are optimised for each patient based on individual inspiratory capacity using a microchip-containing smartcard inserted in the device.

In order to generate the two different lung deposition patterns, we adjusted three characteristics of the nebuliser treatment: particle size, breathing pattern and timing of aerosol bolus (fig. 1).

The investigator carefully instructed each patient on the use of the Akita² at the start of the study. Patients in both treatment arms received instructions and feedback from the display of the Akita² during each nebulisation, to ensure that the correct

Large airway deposition



Small airway deposition

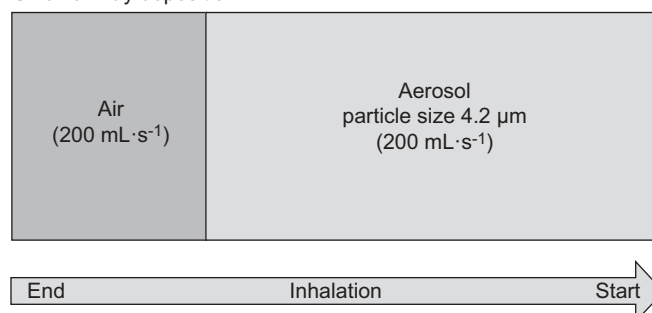


FIGURE 1. Breathing patterns on smartcard.

breathing pattern was performed. Additional details on feedback to the patient and inhalation settings of the device, as well as technical details, can be found in the online supplementary material.

Study end-points

The primary end-point of this study was change in FEF_{75%} (Z-score) after 4 weeks of targeted treatment. Secondary end-points were change in FEF_{75%} (L·s⁻¹), change in FEV₁, FVC, FEF_{25–75%} (Z-score and absolute values), lung clearance index (LCI) and diary symptom scores.

Study visits were scheduled at t=0, 2 and 4 weeks. At each study visit, spirometry tests were performed. Spirometry was measured on a Masterscreen electronic spirometer (Jaeger/Viasys, Würzburg, Germany) according to European Respiratory Society/American Thoracic Society guidelines. LCI measured by a multiple breath washout test (Exhalyzer®D Ecomedics, Duernten, Switzerland) was performed at each visit only in the Sophia Children's Hospital because this test was not available in the other two centres.

Adverse events during the study were recorded in an updated version of a diary used in previous studies (table E2 of the online supplementary material) [31, 32]. Patients were asked to daily record any unusual symptoms and a symptom score comprising items on cough, mucus and shortness of breath. The possible total symptom score for 1 day ranged from 0 to 18 points.

Adherence

The Akita² monitors adherence by recording on the smartcard the date, time and number of breaths of each nebulisation treatment. For each patient, we calculated daily dose adherence, which expresses the percentage of days a patient adhered correctly to the prescribed once daily nebulisation of dornase alfa.

Estimate of sample size

We aimed to detect a 10% difference in FEF_{75%} at the 5% significance level for a two-sided test with 80% power. Based on previous data, this would require 44 patients in total (22 patients in each group) [33]. To anticipate possible dropouts, we aimed to include 25 patients per study arm.

Statistical analysis

Data were analysed on an intention-to-treat basis. Analyses of between-group comparisons regarding change in lung function variables (FVC, FEV₁, FEF_{75%}, FEF_{25–75%} and LCI) were performed using repeated measurements ANOVA with adjustment for baseline values, centre and use of tobramycin solution for inhalation. Changes are reported as mean ± SEM. Analyses were performed with SPSS software (version 15.0; IBM, Chicago, IL, USA). For all analyses, two-tailed p-values were considered to indicate statistical significance when p<0.05. A per-protocol analysis was conducted in which patients who violated the study protocol were excluded. Protocol violations were defined as patients who did not complete the trial, had adherence <70% or for whom adherence data could not be retrieved (fig. 2).

Patients who improved by ≥10% pred for FEF_{75%} were defined as excellent responders. We calculated whether there

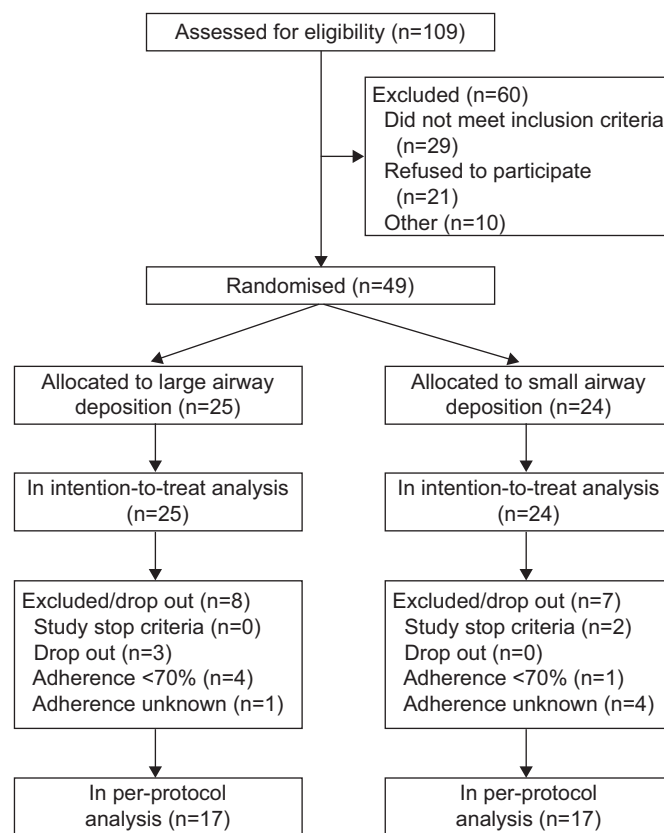


FIGURE 2. Enrolment, random assignment, follow-up and analysis.

was a significant difference between the groups in number of excellent responders using a Chi-squared test with continuity correction.

Spirometry variables were expressed as Z-scores and % pred using the reference values published by STANOJEVIC *et al.* [34] for FVC, FEV₁ and FEF_{25–75%}. Since these reference equations do not include data for FEF_{75%}, we used the reference values published by ZAPLETAL *et al.* [35] for FEF_{25–75%}. Changes in absolute values of spirometry variables (L and L·s⁻¹) were expressed as percentage of baseline values.

For each patient, mean daily symptom scores per week were computed. When <4 out of 7 days of a week were recorded, scores for that week were regarded as not evaluable. Differences in number of adverse events and changes in diary scores were analysed using a Mann–Whitney test and Chi-square test.

RESULTS

49 patients were included in the study, 44 of whom completed the trial (22 patients in each group). All patients were enrolled between September 2007 and March 2010. Baseline characteristics of patients in the two treatment groups were similar (table 1). Mean treatment time for the high lung dose of dornase alfa that was delivered during this study was 11 min 51 s for the large airways group and 9 min 27 s for the small airways group. Difference in treatment time between the groups was not significant (p=0.13).

TABLE 1 Baseline characteristics of patients in each treatment group

Variables	Large airways	Small airways
Subjects	25	24
Sex males/females	14/11	12/12
Age yrs	13.3±3.4	12.7±3.5
Height cm	153.5±16.5	153.4±18.1
BMI kg·m ⁻²	18.7±2.7	18.2±2.2
Pancreatic insufficiency yes/no	22/3	20/4
Chronic <i>P. aeruginosa</i> yes/no	10/15	9/15
Maintenance inhaled tobramycin yes/no	9/16	8/16
CF mutation homozygous delF508/other	15/10	10/14
FVC Z-score	-0.5±1.2	-0.7±1.5
FVC % pred	94.6±13.1	91.7±17.1
FEV ₁ Z-score	-1.6±1.1	-1.7±1.3
FEV ₁ % pred	81.8±13.1	80.4±15.6
FEF _{25-75%} Z-score	-2.2±1.2	-2.3±1.2
FEF _{25-75%} % pred	55.5±19.6	54.7±19.9
FEF _{75%} Z-score	-5.2±2.7	-5.5±2.7
FEF _{75%} % pred	39.7±17.4	37.2±16.0
LCI absolute values	8.7±1.6 [#]	9.9±1.8 [†]

Data are reported as n or mean±sd. BMI: body mass index; *P. aeruginosa*: *Pseudomonas aeruginosa*; CF: cystic fibrosis; FVC: forced vital capacity; % pred: % predicted; FEV₁: forced expiratory volume in 1 s; FEF_{25-75%}: forced expiratory flow between 25% and 75% of FVC; FEF_{75%}: forced expiratory flow at 75% of FVC; LCI: lung clearance index. [#]: n=15; [†]: n=14.

Lung function (intention-to-treat analysis)

FEF_{75%} improved substantially and significantly in both groups after 4 weeks of treatment (table 2 and fig. 3a): by 0.7 sd (p=0.03) in the large airways group and by 1.2 sd (p=0.001) in the small airways group. This corresponds to

an improvement of 5.2% and 8.8% pred, respectively. The difference in mean FEF_{75%} between both groups was 0.4 sd (95% CI -0.4–1.2 sd; p=0.31) for small airways *versus* large airways deposition.

A similar effect was observed for FEF_{25-75%} (table 2). FVC and FEV₁ did not change significantly in both groups, and the difference in FEV₁ or FVC between the groups after 4 weeks of treatment was not significant.

FEF_{75%} improved by ≥10% pred in four (18%) out of 22 patients in the large airways group and in 10 (45%) out of 22 patients in the small airways group. The difference in number of excellent responders between the groups was not significant (p=0.10).

LCI was measured in 29 patients: 15 in the large airways and 14 in the small airways group. LCI did not change significantly in either group over 4 weeks, nor was there a significant difference between the groups in the change in LCI (table 2).

Symptom scores

Mean symptom score per day in week 1 was 1.8±1.9 points for the large airways group and 2.9±2.3 points in the small airways group. Symptom scores were slightly lower in the first week of the study in the large than the small airways group (p=0.05). Mean symptom scores during the rest of the study did not significantly differ between treatment groups and there were no significant changes within either group (table E3 of the online supplementary material).

FEF_{75%} (per-protocol analysis)

15 out of the 49 patients were excluded from the per-protocol analysis: five patients did not complete the trial, five patients had a daily dose adherence <70% and, for five patients, data on adherence could not be retrieved (fig. 2). As a result, 17 patients in each group were analysed for the primary end-point (FEF_{75%}).

TABLE 2 Lung function after 4 weeks of study treatment

Variables	Large airways ITT [#]		Small airways ITT [†]		Mean difference ITT
	Z-score	L·s ⁻¹ % BL	Z-score	L·s ⁻¹ % BL	Z-score (95% CI)
FEF _{75%}	0.7±0.3*	24.1±10.3*	1.2±0.3*	35.3±10.1*	0.4 (-0.4–1.2)
FVC	0.0±0.1	1.4±1.5	0.1±0.1	2.4±1.5	0.0 (-0.2–0.3)
FEV ₁	0.2±0.1	3.6±2.1	0.1±0.1	3.5±2.1	-0.1 (-0.4–0.3)
FEF _{25-75%}	0.4±0.1*	14.8±6.4*	0.3±0.1*	16.1±6.3*	-0.1 (-0.5–0.3)
LCI	-0.1±0.5 [‡]		-0.3±0.5 [§]		0.5 (-0.7–1.7)
Variables	Large airways PP ^f		Small airways PP ^f		Mean difference PP
	Z-score	L·s ⁻¹ % BL	Z-score	L·s ⁻¹ % BL	Z-score (95% CI)
FEF _{75%}	0.7±0.3*	17.3±7.5* ^{##}	1.4±0.3*	37.5±7.5* ^{##}	0.7 (-0.1–1.5)

Data are presented as mean±SEM change from baseline (ANOVA estimates), unless otherwise stated. Difference is shown for small airways minus large airways group (Z-score and 95% CI). ITT: intention-to-treat analysis; % BL: % change from baseline; FVC: forced vital capacity; FEF_{75%}: forced expiratory flow at 75% of FVC; FEV₁: forced expiratory volume in 1 s; FEF_{25-75%}: forced expiratory flow between 25% and 75% of FVC; LCI: lung clearance index; PP: per-protocol analysis. PP analysis was performed only for the primary end-point, FEF_{75%}. [#]: n=25; [†]: n=24; [‡]: n=15; [§]: n=14; ^f: n=17. *: p≤0.05 for change from baseline within treatment group; ^{##}: p≤0.05 for difference between treatment groups.

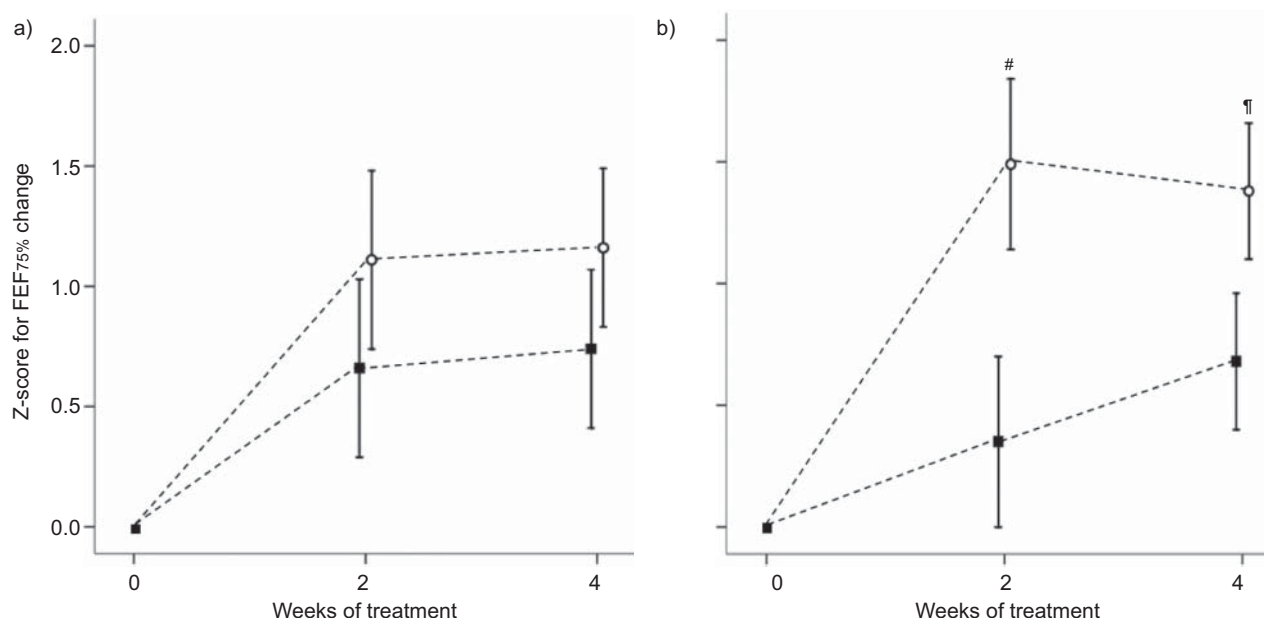


FIGURE 3. Mean changes from baseline for forced expiratory flow at 75% of forced vital capacity (FEF75%) (Z-score) after 2 and 4 weeks of treatment. a) Intention-to-treat analysis; b) per-protocol analysis. Data are presented as mean \pm SEM (ANOVA estimates). Closed squares represent large airway deposition, open circles represent small airway deposition. #: $p=0.03$; †: $p=0.06$, for small versus large airway deposition.

FEF75% improved significantly in both groups after 4 weeks of treatment: by 0.7 SD (95% CI 0.1–1.2 SD; $p=0.02$) in the large airways group, and by 1.4 SD (95% CI 0.8–1.9 SD; $p<0.001$) in the small airways group (table 2). These increases in Z-scores correspond with improvements of 5.6% and 10.7% pred, respectively. Analysis of change in absolute values of FEF75% ($L \cdot s^{-1}$ and expressed as percentage of baseline) demonstrated that FEF75% improved by 17.3% (95% CI 2.1–32.6%; $p<0.001$) in the large airways group and by 37.5% (95% CI 22.2–52.8%; $p<0.001$) in the small airways group.

After 2 weeks of treatment, the difference in FEF75% between the groups was 1.2 SD (95% CI 0.1–2.2 SD; $p=0.03$) in favour of the small airways group. After 4 weeks, the difference was 0.7 SD (95% CI -0.1–1.5 SD; $p=0.06$) in favour of the small airways group (fig. 3b). Expressed as absolute values, the difference in FEF75% in favour of small airways deposition was 32.4% (95% CI 3.4–61.4%; $p=0.03$) after 2 weeks and 21.3% (95% CI 1.4–41.2%; $p=0.04$) after 4 weeks of treatment (data shown in figure E1 of the online supplementary material).

Adverse events

A total of 31 adverse events were reported during the study, 18 in the large airways group and 13 in the small airways group. There was no statistically significant difference in number of adverse events between the groups ($p=0.90$).

In general, adverse events were either self-limiting symptoms (e.g. runny nose and headache) or symptoms consistent with CF (e.g. respiratory infections and bowel problems). Three adverse events were considered to be possibly related to the study intervention: three patients in the large airways group experienced hoarseness for 1 or 2 days during the first 2 weeks of the study. Temporary hoarseness is a known side-effect of dornase alfa inhalation. In these patients the symptoms

resolved spontaneously. No serious adverse events were reported in either group.

DISCUSSION

To our knowledge, this is the first randomised double-blind controlled trial comparing large airway *versus* small airway deposition of inhaled dornase alfa using a smart nebuliser system. We observed a substantial and statistically significant improvement in spirometry indicators of small airway patency in both groups. The per-protocol analysis, but not the intention-to-treat analysis, demonstrated better treatment response in the small airways group.

The most striking finding in this study is that both treatment groups showed considerable improvement in FEF75% and FEF25–75%, indicating improved patency of the small airways, within 4 weeks of switching from a conventional nebuliser to a smart nebuliser for their daily dornase alfa inhalation. Mean improvement in FEF25–75% after 4 weeks of treatment for all patients, independent of deposition group, was 5.9% pred. This is remarkable, because all patients were on maintenance treatment with the same nominal dose of dornase alfa prior to the study. It is noteworthy that this improvement is relatively large compared with the 8.4% improvement in the PEIT study [13], which included dornase alfa-naïve patients who were randomised to 2.5 mg dornase alfa or placebo once daily with a conventional jet nebuliser. Our study included only patients who were already on maintenance dornase alfa treatment and we simply changed the nebuliser. Hence, the present study suggests that the efficacy of the same medication can be improved by another 70% simply by optimising adherence and inhalation technique.

There are a few explanations for this improvement of small airway function. One likely explanation is that adherence to

dornase alfa treatment was higher during the study than before it. Overall adherence to once daily dornase alfa nebulisation was 85% during the study and thus probably above daily routine. It is well-known that adherence to chronically inhaled medication is in the order of 40–60% in CF patients and is higher during clinical trials [36–38]. However, we feel that the improvement in FEF75% is too large to be caused by improved adherence only.

A second likely explanation for the improvement in FEF75% in both groups is the controlled inhalation technique of the smart nebuliser. The Akita² device directs inspiratory flow and inhaled volume during each breath and coaches patients to perform the correct breathing manoeuvre. Consequently, the use of this device increases total lung dose of dornase alfa, improves small airways deposition and reduces loss of aerosol into the environment [21, 24–26].

A third explanation is the higher lung dose delivered during study treatment. Before enrolment in this study, 84% of the patients used a conventional jet nebuliser for their maintenance treatment (table E4 of the online supplementary material). These nebulisers have poor efficiency, delivering only 10–20% of the loaded dose to the lungs [27–30]. Up to 50% of the drug is retained in the nebuliser at the end of nebulisation, and 20% of the nominal dose is lost to the environment [28]. The smart nebuliser used in our study delivers up to 70% of the nominal dose to the lungs [24, 26].

At the time of the registration studies of dornase alfa several dose finding studies were performed. Daily doses varying between 2.5 and 20 mg were given to patients in phase II and III trials without observing a dose-dependent response in FEV1 or FVC [11, 39]. All doses were safe. Unfortunately, these studies did not report the effect of the various treatment regimens on FEF75% or FEF25–75%.

The other important new finding of this study is that increased delivery of dornase alfa to small airways is possible, as demonstrated by greater FEF75% and FEF25–75% responses in both treatment groups, and that doing so seems to be safe. Small airway deposition was accomplished by reducing aerosol particle size and nebulising drug early during deeper inhalation, but even the large airways group benefitted from an increased peripheral deposition. The intention-to-treat analysis did not show a difference between the two deposition groups. This might be explained by the fact that the use of a breath-actuated and efficient nebuliser in this population with relatively mild airway obstruction resulted in substantially more drug reaching the large surface area of the small airways than when using a conventional jet nebuliser, even for the central airways deposition settings. This might have resulted in reaching the plateau of the dose–response curve in both groups and thus not finding a significant difference between the two deposition groups.

However, the per-protocol analysis demonstrated greater improvement and a significant difference between the groups for FEF75% ($L \cdot s^{-1}$) in favour of the small airways group. This “best case scenario” analysis illustrates the potential of optimising every possible aspect of dornase alfa therapy, *i.e.* optimal delivery to the small airways and optimal adherence. The clinical relevance of our study is that it underlines that both

adherence and inhalation competence are important determinants for the optimisation of the treatment effect of dornase alfa. Clearly, the use of a breath-actuated efficient nebuliser for maintenance treatment of dornase alfa should be considered “off-label treatment”. However, nowadays most patients use off-label nebulisers because these are different from the ones used in the registration studies for dornase alfa almost two decades ago. We feel that a breath-actuated efficient nebuliser is a promising treatment option that should be considered, especially for those patients with progressive small airway disease or possible poor competence and/or adherence.

Two previous large, open-label studies in dornase alfa-naïve patients compared the efficacy of small *versus* larger particles and showed a similar trend as in this study, but were not conclusive [40, 41]. The most likely explanation for these negative findings was the use of conventional jet nebuliser systems. Standard jet nebulisers produce an aerosol with a wide range of particle sizes and a relatively large mean particle size. Large aerosol particles have a high probability for deposition in the central airways. Furthermore, most patients perform tidal breathing while using a standard nebuliser. This leads to preferential deposition of particles in the large airways. In contrast, a slow and deep inhalation increases the probability of particle deposition in the small airways. Therefore, the conditions in these two studies probably were not optimal for delivery of the drug to the small airways. An open-label, single-arm study on bolus inhalation of dornase alfa by GELLER *et al.* [42] showed the importance of breath control during nebulisation. In this study, CF patients were treated with a device that was breath actuated, delivered an aerosol bolus when the optimal inspiratory flow rate was achieved and generated visual cues for the subject to inhale deeply within the optimum range of inspiratory flow rates. FEV1 and FEF25–75% significantly improved after 2 weeks of dornase alfa treatment using the study device. Our study supports the conclusions by GELLER *et al.* [42], that controlled and deep inhalation is important in order to achieve optimal treatment effect.

It is likely that the optimised inhalation technique used in our study could also benefit patients with other respiratory diseases, such as chronic obstructive pulmonary disease or asthma. However, this should be confirmed by clinical trials conducted in these patient groups.

In conclusion, our study shows that 4 weeks of dornase alfa nebulised using a state-of-the-art nebuliser device resulted in a significant improvement in FEF75% and FEF25–75% in children with stable CF who were on prior maintenance treatment with dornase alfa. In children with good adherence (per-protocol analysis), greater treatment response was observed for small airway deposition compared with large airway deposition.

CF is a fatal disease and its main cause of death is loss of lung function with respiratory failure. Every option to improve lung function and to reduce its rate of decline should be utilised in order to improve its long-term prognosis. This study suggests that better treatment response and further improvement of small airway function is indeed feasible by optimising the inhalation technique for administration of a known and effective mucolytic drug, using an efficient nebuliser and breath-control technology.

CLINICAL TRIAL

This study is registered at www.trialregister.nl and in the International Standard Randomised Controlled Trial Number Register with identifier number 6422851.

STATEMENT OF INTEREST

Statements of interest for E.M. Bakker, B.M. Assael and H.A.W.M. Tiddens, and for the study itself, can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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