

# A Crossover, Randomized, Controlled Trial of Dornase Alfa Before Versus After Physiotherapy in Cystic Fibrosis

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**ABSTRACT.** *Objective.* Although dornase alfa is a widely used, aerosolized, mucolytic agent in patients with cystic fibrosis (CF), its efficacy in relation to the timing of physiotherapy has not been tested. We sought to determine whether dornase alfa is more efficacious when it is administered 30 minutes before versus 30 minutes after physiotherapy/positive expiratory pressure (PEP) therapy in clinically stable children.

*Methods.* Using a crossover, randomized, double-blind, and placebo-controlled trial, we undertook a 6-week study of the efficacy of dornase alfa in relation to the timing of physiotherapy at home. There were 2 treatment orders. Dornase alfa before + placebo after physiotherapy/PEP for 2 weeks was followed by a 2-week washout and then the reverse order placebo before and dornase alfa after physiotherapy/PEP for the final 2 weeks. The second treatment order reversed the placebo and dornase alfa therapy for the first and last 2-week blocks. The main outcome measures used included the change in predicted percentage of forced expiratory volume in 1 second (FEV<sub>1</sub>), a composite quality of well-being score (QWB), and a measure of aerobic fitness (maximal oxygen consumption, [VO<sub>2max</sub>]), determined using shuttle testing.

*Results.* Fifty-two patients who had CF (27 female) with mild to moderate suppurative lung disease, were a mean ± SD age of 10.7 ± 3.2 years, had Shwachman scores of 86 ± 11.8, had predicted FEV<sub>1</sub> of 83% ± 18%, had quality of well-being score of 0.76 ± 0.08, and had VO<sub>2max</sub> of 42.6 ± 6.3 ml/kg per min were enrolled. Fifty patients completed the study. Intention-to-treat analysis was used. Nonsignificant mean (95% confidence interval) differences in FEV<sub>1</sub> (0.02 L [−0.05 to 0.10]), VO<sub>2max</sub> (−0.75 ml/kg per min [−1.85 to 0.35]), and QWB (0.005 [−0.94 to 0.0028]) for dornase alfa after physiotherapy/PEP were detected. A post hoc analysis showed that patients who were colonized persistently with *Pseudomonas aeruginosa* had a significantly greater improvement in FEV<sub>1</sub> (0.12 L [0.23 to 0.01] vs −0.04 L [0.05 to −0.13]) when dornase alfa was administered after physiotherapy/PEP.

*Conclusions.* Dornase alfa is equally efficacious when delivered before or after physiotherapy/PEP in patients with CF. Patients who are colonized persistently with *P aeruginosa* may derive more improvement in

FEV<sub>1</sub> when dornase alfa is delivered after physiotherapy/PEP. *Pediatrics* 2005;116:e549–e554. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2005-0308](http://www.pediatrics.org/cgi/doi/10.1542/peds.2005-0308); *dornase alfa, efficacy, physiotherapy.*

ABBREVIATIONS. CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in 1 second; PEP, positive expiratory pressure; VO<sub>2max</sub>, maximal oxygen consumption; QWB, quality of well-being score; CI, confidence interval; FEF<sub>25–75</sub>, mid expiratory flow rate.

Physiotherapy and systemic and nebulized antibiotics have been the cornerstones of treatment in cystic fibrosis (CF) for many years.<sup>1–3</sup> The introduction of the nebulized mucolytic agent dornase alfa (Pulmozyme [Hoffman-La Roche, Dee Why, Sydney, Australia]) in the 1990s proved to be an innovative adjunct to the management of lung disease in terms of reduced pulmonary exacerbations, improved lung function, and quality-of-life measures.<sup>3–5</sup> Dornase alfa use varies from country to country, on the basis of patient preference, physician prescribing practices, measured benefit in an individual, and health funding arrangements. In Australia, most recent figures indicate that dornase alfa is used by 22.1% of school-aged children (5–18 years), all of whom have demonstrated a >10% improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>) after 4 weeks of therapy.<sup>6</sup>

However, despite the evaluation of dornase alfa in >15 years of clinical trials, there is no evidence as to whether dornase alfa is more efficacious when delivered before or after physiotherapy. As has been shown in adults who are prescribed dornase alfa, patients and families will vary their therapies because of time constraints.<sup>7</sup> Thus, it is important to establish whether this will have an impact on their response to therapy. Although the dornase alfa product information leaflet suggested that its administration could precede or follow physiotherapy, we could find no evidence to support the majority of our patients' preferring to use the medication before physiotherapy. Consequently, we sought to determine whether the use of dornase alfa was equally efficacious whether used before or after physiotherapy in clinically stable, school-aged children with CF and mild to moderate suppurative lung disease.

## METHODS

Participants were recruited from patients who had attended the CF outpatient clinics at the Children's Hospital at Westmead, Sydney, and the John Hunter Children's Hospital, Newcastle, in

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New South Wales, Australia. To be eligible, participants had to be of school age (5–18 years), able to perform spirometry reliably, have clinical or radiologic evidence of mild to moderate suppurative lung disease, have an FEV<sub>1</sub> <90% predicted and an forced vital capacity (FVC) >40% predicted, live within 100 km of the institution where testing would be performed, and be willing to attend four 60-minute outpatient visits over a 6-week period. Exclusion criteria were a previous trial of dornase alfa within the last 12 months, current use of dornase alfa, and involvement in another clinical trial within the last 4 weeks. In Australia, dornase alfa is not government subsidized for children who are too young to perform spirometry. The study was approved by the Ethics Review Committees of the Children's Hospital at Westmead and the John Hunter Children's Hospital.

Participants were randomized to 1 of 2 treatment orders for the administration of dornase alfa either 30 minutes before daily physiotherapy/positive expiratory pressure (PEP) mask therapy or 30 minutes after physiotherapy/PEP mask therapy. Patients who used a PEP mask instead of physiotherapy routinely were asked to continue the same practice throughout the 6 weeks of the study. Similarly, participants were requested to continue to have once-daily physiotherapy/PEP mask therapy at the same time of day throughout the study. There were 2 treatment orders, each with a 2-week washout between active treatments (Fig 1).

At visit 1, all participants underwent a physical examination to assess their clinical status, and their medical records were reviewed to ascertain their last Shwachman score<sup>8</sup> (within the preceding 12 months) and sputum culture results over the last 12 months and to document comorbidity such as hemoptysis or CF-related diabetes. At each visit, participants underwent spirometry according to American Thoracic Society criteria<sup>9</sup> using the derived predicted values of Polgar and Promadhat<sup>10</sup> and a shuttle test (20 m for those older than 7 years or a 10 m for those aged 5–7 years) to estimate their maximal aerobic capacity (VO<sub>2max</sub>)<sup>11</sup> and completed a composite (mobility scale and physical and social activity scales) quality of well-being score (QWB).<sup>12</sup> Participants completed a diary card documenting the time of day that medications were administered (AM or PM) and returned all ampoules (dornase alfa and placebo) for a count-back of medications used to assess compliance.

Participants were assessed by 1 of 2 research officers. The research officers had assessed the first 4 participants concurrently and agreed on standardized assessment procedures for conducting the shuttle tests. For assessing the response to the timing of dornase alfa, results after 2 weeks of medication before physiotherapy were compared with results of 2 weeks after physiotherapy (ie, visits 2 and 4) as any improvement in FEV<sub>1</sub> after 14 days of dornase alfa therapy dissipates within an additional 14 days off treatment.<sup>13</sup>

Previous work has documented a 4% to 6% improvement in FEV<sub>1</sub> after 6 months of treatment with dornase alfa for school-

aged children who complied with therapy.<sup>4</sup> For this study, a change in percentage of predicted FEV<sub>1</sub> of 5% (~0.08 L at 10 years of age), equivalent to a 0.5 SD change over baseline, was chosen as a clinically significant improvement in FEV<sub>1</sub>. Using an  $\alpha$  of .05 and 99% power, we needed to recruit a total of 49 participants. Given randomization blocks of 4 patients, 52 patients were needed.

Treatment was allocated in randomization blocks of 4 from the Children's Hospital at Westmead pharmacy. Randomization was completed using a table of random numbers, allocating treatment order 1 to even numbers and treatment order 2 to odd numbers. Allocation concealment was achieved through the dispensing hospital pharmacy. Patients, investigators, and outcomes assessors were blinded to the treatment allocation. Patients at visits 1, 2, and 3 received 2 color-coded boxes that each contained 14 nebulizer ampoules that were labeled "Before" and "After" physiotherapy. The placebo and dornase alfa ampoules were similar in appearance, color coding, and individual labeling as "Before" or "After."

All analyses were performed using SAS software (version 6.12). Formal inferential statistical methods were applied to outcome measures, and descriptive statistics were used for continuous data. Intention-to-treat analysis was used. The crossover differences for preshuttle FEV<sub>1</sub>, VO<sub>2max</sub>, and QWB were analyzed to test for a difference in these parameters when dornase alfa was administered before physiotherapy/PEP therapy compared with after physiotherapy/PEP therapy. As the crossover differences for FEV<sub>1</sub>, VO<sub>2max</sub>, and W all were normally distributed, they were analyzed using a *t* test adjusting for a period effect using the Hills Armitage Approach.<sup>14</sup> A statistically significant difference was inferred for *P* < .05.

## RESULTS

Participants were recruited concurrently from the 2 hospital CF outpatient clinics. Fifty-two patients were recruited, and 50 completed the study. The 2 withdrawals came from treatment order 2. Both patients (10-year-old girl withdrew on day 43, and 9-year-old boy withdrew on day 14) were withdrawn for protocol violations as they had taken only 1 medication and had chosen to give this either before or after physiotherapy according to parental preference. A total of 365 patients were identified in the combined 2-hospital CF patient registry, which included all patients who had attended the outpatient clinic on at least 1 occasion between 1998 and 2000. Of these, 313 of patients were excluded (Fig 2). Of the 313 patients, 216 (69%) did not meet study inclusion criteria: 95 were not between 5 and 18 years of age, 56

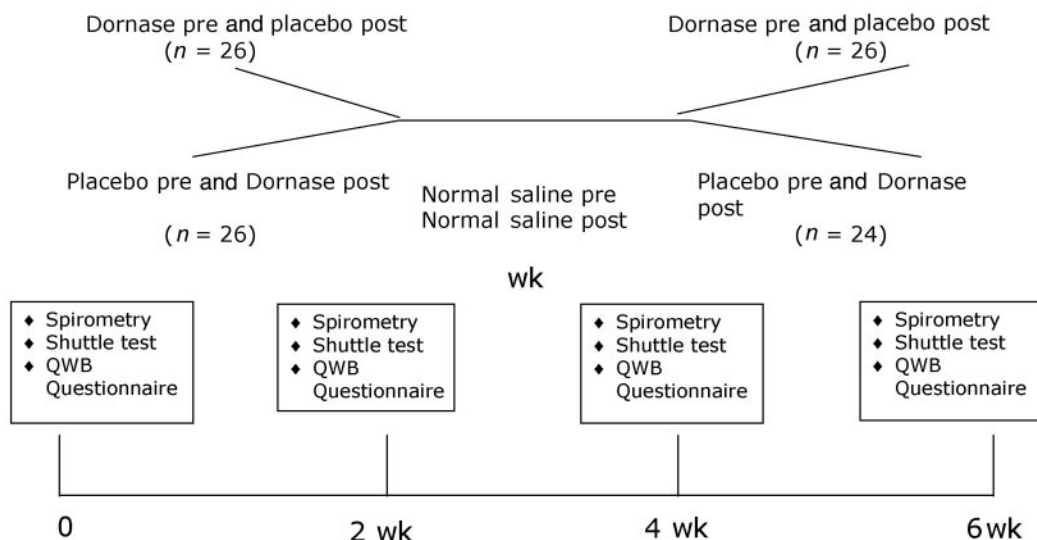


Fig 1. Study design: patients were randomized to 1 of 2 treatment orders that consisted of three 2-week treatment blocks that encompassed 4 clinical assessments. "Pre" refers to therapy (dornase alfa or placebo) administered 30 minutes prior to physiotherapy, and "post" refers to dornase alfa or placebo administered 30 minutes after physiotherapy.

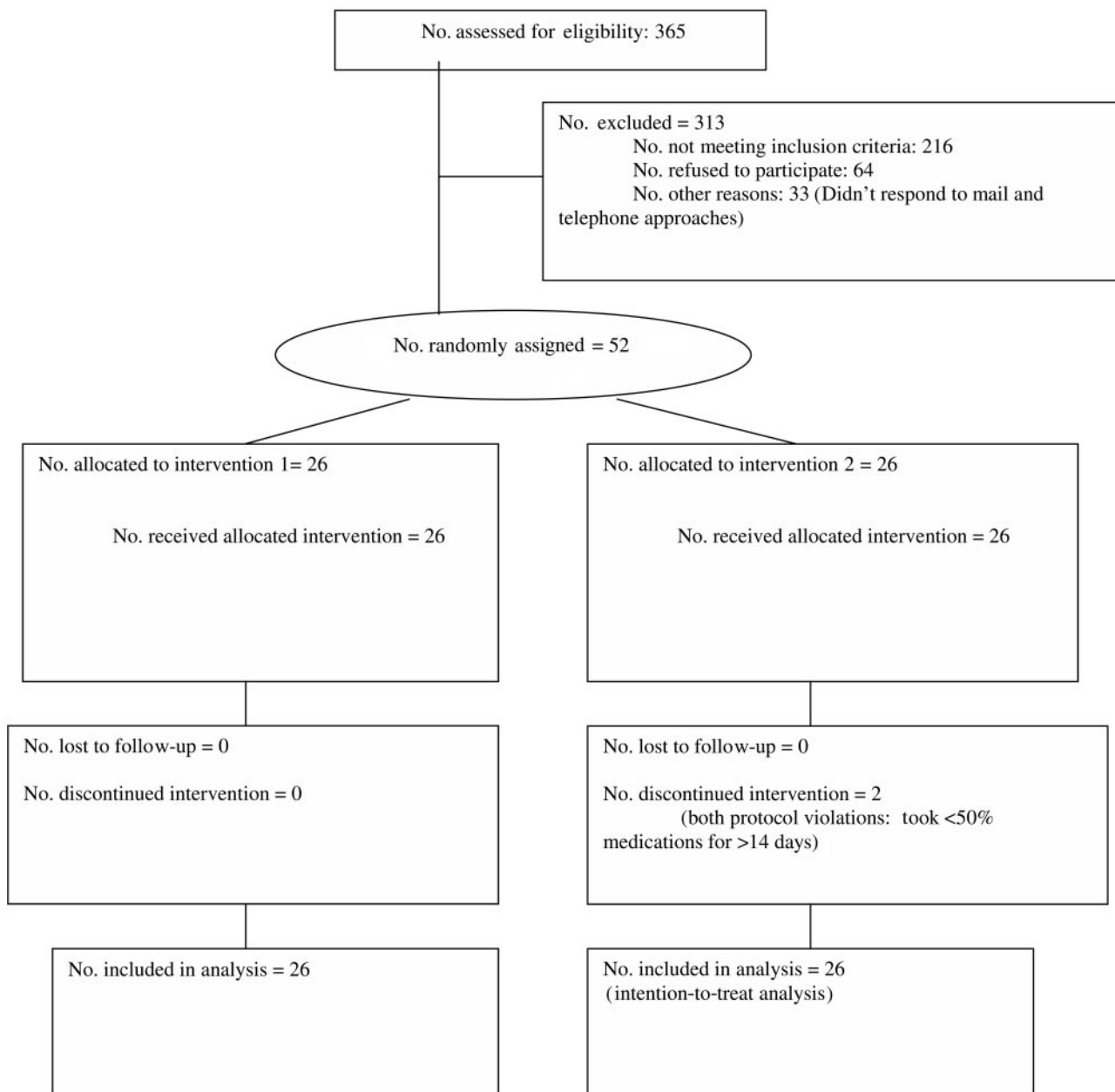


Fig 2. Trial profile: flow diagram of patient retention through the study.

lived >100 km from a study center, 37 were already using dornase alfa, 23 met other criteria but had normal lung function ( $FEV_1 > 90\%$  predicted), and 5 had unsuccessfully tried dornase alfa in the preceding 6 months. Sixty-four (20.5%) patients refused to participate, and 33 (10.5%) did not respond to mail and telephone invitations to participate. Fifty-two participants were randomized to treatment order 1 ( $n = 26$ ) or treatment order 2 ( $n = 26$ ). There were 27 female patients. However, both patients who discontinued were included with the 50 patients who completed the study in the intention-to-treat analysis. The mean ( $\pm$ SD) age was  $10.7 \pm 3.2$  years, Shwachman score was  $86 \pm 11.8$ , % predicted  $FEV_1$  was  $83 \pm 18\%$ , W was  $0.76 \pm 0.08$ , and  $VO_{2max}$  was  $42.6 \pm 6.3$  ml/kg per min.

Thirty-five (67%) of the 52 patients had >10% im-

provement in their  $FEV_1$  with dornase alfa over one 2-week treatment block. Of the 35 patients, 18 had >10% improvement in  $FEV_1$  during the first treatment period (between visits 1 and 2), and 17 had >10% improvement in  $FEV_1$  during the second treatment period (between visits 3 and 4). Age, baseline  $FEV_1$ , weight, and treatment order did not influence the likelihood of a >10% in  $FEV_1$  in response to dornase alfa. In contrast, only 8 patients had >10% improvement in  $FEV_1$  over both 2-week treatment periods.

The primary outcome measure was the change in the preshuttle  $FEV_1$  as determined by the least squares mean (which is the mean crossover difference), adjusting for imbalance between the 2 treatment sequences, when an unequal number of observations occur in each treatment sequence. There was

a statistically nonsignificant least mean squares crossover difference of 0.02 L when dornase alfa was administered after physiotherapy/PEP mask therapy compared with dornase alfa before physiotherapy/PEP mask therapy (95% confidence interval [CI]:  $-0.05$  to  $0.10$ ;  $P = .52$ ; Fig 3). There were no statistically significant differences in the FVC or the mid-expiratory flow ( $FEF_{25-75}$ ).

The secondary outcome measures included the change in  $VO_{2max}$  and change in the QWB. A least squares mean crossover difference of  $-0.75$  ml/kg per min was demonstrated in aerobic capacity, for dornase alfa administered after physiotherapy/PEP mask therapy compared with dornase alfa administered before physiotherapy/PEP mask therapy, but the change was not statistically significant (95% CI:  $-1.85$  to  $0.35$ ;  $P = .174$ ). Similarly, a statistically nonsignificant least squares mean crossover difference of  $.005$  was demonstrated in the QWB for dornase alfa administered after physiotherapy/PEP mask therapy compared with dornase alfa administered before physiotherapy/PEP mask therapy (95% CI:  $-0.019$  to  $0.028$ ;  $P = .698$ ). A significant period effect was demonstrated in QWB ( $P = .03$ ), suggesting that on average a higher quality of well-being was achieved in period 1 (visit 2: least squares mean =  $0.778$ ; standard error =  $0.008$ ), compared with period 2 (visit 4: least squares mean =  $0.752$ ; standard error =  $0.008$ ).

A post hoc subgroup analysis was conducted on the primary outcome measure,  $FEV_1$ , according to whether patients were colonized nonexclusively with *Pseudomonas aeruginosa* for the 2 years before enrollment in the study. Colonization was defined as 2 or more sputum samples per year that grew mucoid and/or nonmucoid *P aeruginosa*. A significant ( $P = .034$ ) least squares mean crossover difference of  $0.12$  L (95% CI:  $0.01$ – $0.23$ ) in  $FEV_1$  (average 6% increase on baseline) for participants who were colonized chronically with *P aeruginosa* ( $n = 17$ ) compared with a difference of  $-0.04$  L (95% CI:  $0.13$ –

$0.05$ ) for those with no or intermittent colonization ( $\leq 1$  positive culture for mucoid *P aeruginosa* per year) with mucoid *P aeruginosa* ( $n = 35$ ) was demonstrated for after physiotherapy/PEP mask therapy compared with before physiotherapy/PEP mask therapy  $FEV_1$  (Fig 4).

There were 34 adverse events reported in 26 participants (50%). Viral upper respiratory tract infections and exacerbations of suppurative lung disease with previously isolated sputum pathogens accounted for 27 of 34 events, which included 1 patient with an exacerbation of asthma. Three participants required hospital admission for intravenous antibiotic treatment of infection, 2 for exacerbations of suppurative lung disease, and 1 with streptococcal septicemia. Musculoskeletal injuries sustained during usual sporting activities accounted for 4 of 34 adverse events, and gastrointestinal complaints (dyspepsia and distal intestinal obstruction syndrome) accounted for the remaining 3 of 34 events.

## DISCUSSION

This study has demonstrated that dornase alfa is equally efficacious whether applied 30 minutes before or after physiotherapy in terms of quality-of-life measures, lung function, and aerobic fitness in children who have CF who have mild to moderate suppurative lung disease. The findings in the study have raised the possibility that individual patients may respond differently to dornase alfa when administered before versus after physiotherapy over a 2-week period. It is interesting that the study demonstrated (in a post hoc analysis) that patients who are colonized with *P aeruginosa* may gain a greater improvement in  $FEV_1$  when dornase alfa is administered after physiotherapy.

Although dornase alfa has been shown to be efficacious in improving  $FEV_1$  in childhood, the response is not universal.<sup>15</sup> Even when dornase alfa is demonstrated to improve lung function in an individual, adherence to therapy is often less than the physician presumes.<sup>7</sup> Consequently, the demonstration in this study of equal utility of dornase alfa before or after physiotherapy provides the first evidence for the clinician to advocate more flexibility with this therapy in relation to physiotherapy, which

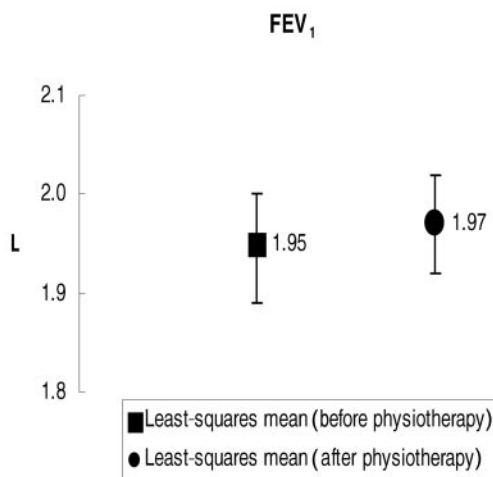


Fig 3. The primary outcome measure, change in  $FEV_1$ , was unaffected whether dornase alfa was administered before or after physiotherapy ( $N = 52$ ;  $P = .052$ ).

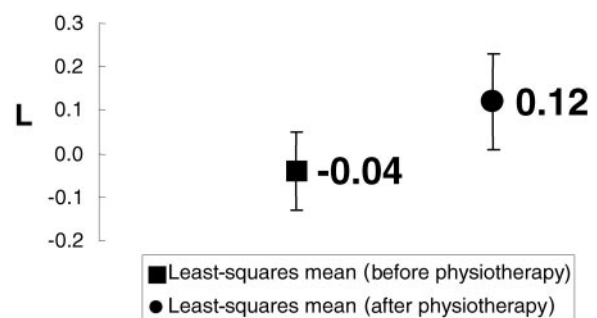


Fig 4. A post hoc analysis demonstrated a significantly greater improvement in  $FEV_1$  for 17 patients who were colonized chronically with *P aeruginosa* compared with 35 patients with intermittent or no *P aeruginosa* when dornase alfa was administered 30 minutes after physiotherapy ( $0.12$  L [95% CI:  $0.23$ – $0.01$ ] vs  $-0.04$  L [95% CI:  $0.05$  to  $-0.13$ ];  $P = .034$ ).

may in turn increase adherence as young people who are moving toward adulthood feel encouraged by taking a more active say in their therapeutic regimens.<sup>7,16</sup> In addition, the individual response of a patient to a therapeutic trial of dornase alfa may differ when used before or after physiotherapy as shown in this study. Although a standardized trial of dornase alfa is considered to be 4 weeks, previous work has shown that a therapeutic response can be seen within 2 weeks and dissipate within 2 weeks.<sup>13</sup> Consequently, it may be prudent to consider the timing of dornase alfa in relation to physiotherapy if a 4-week clinical trial proves unsuccessful. This could be achieved by repeating lung function testing after 2 weeks to measure the response and, if <10% improvement in FEV<sub>1</sub>, switching the timing of dornase alfa treatment in relation to physiotherapy. Alternatively, one could standardize the timing of therapy for the full 4 weeks and retry subsequently with alternate timing if the trial were unsuccessful.

There was no alteration in maximal aerobic capacity in our cohort with the interventions. Given that the patients well were nourished and had only mild to moderate suppurative lung disease with a mean FEV<sub>1</sub> of 83% predicted at 10 years of age, they were in reasonably good health. Their average VO<sub>2max</sub> of 42 ml/kg per min, derived indirectly from shuttle testing, is consistent with previously published results derived in similar patients with CF using cycle ergometry and shuttle testing.<sup>11,17,18</sup> The mean VO<sub>2max</sub> results are reassuring for the group of patients. Equally, the lack of change over a 2-week period would not be expected with clinically stable patients who have relatively normal VO<sub>2max</sub> values and did not undergo any exercise training between assessments. In contrast, it has been shown that patients who have CF with more severe lung disease and pulmonary exacerbations and undergo a hospital admission for intravenous antibiotics, physiotherapy, and aerobic training can increase their QWB by 15% and their VO<sub>2max</sub> by 20% within 6 weeks.<sup>19</sup>

The statistically significant average increase in FEV<sub>1</sub> of 6% (0.12 L) for patients who used dornase alfa after physiotherapy and were persistently colonized with nonmucoid and mucoid *P aeruginosa* compared with patients with intermittent nonmucoid and mucoid *P aeruginosa* was an unexpected finding that was independent of baseline FEV<sub>1</sub>, age, or treatment order. The finding is consistent with studies that suggest a more rapid decline in lung function after sputum colonization with *P aeruginosa*<sup>20,21</sup> in that greater access for dornase alfa to distal airways may be achieved if the medication is delivered after physiotherapy, which in turn would potentiate the mucolytic effects of dornase alfa.<sup>22</sup> As a finding in a post hoc analysis, the result warrants additional investigation before it could be recommended as a therapeutic directive.

There are a number of limitations to this study. Although this was an adequately powered study to address a change in FEV<sub>1</sub>, the patients who participated in the study were in the milder range of disease severity and the results may not be generalized to patients with more severe disease. It is interesting

that there were a number of patients (3 of 8 who responded in both treatment orders) who had a baseline FEV<sub>1</sub> between 80% and 90% predicted and demonstrated >10% increase in FEV<sub>1</sub>. This group with milder lung disease may be considered by some clinicians to be "too mild" to justify a trial of dornase alfa, yet some patients in the present study with an FEV<sub>1</sub> >80% predicted demonstrated >10% improvement in their FEV<sub>1</sub>. This result would be consistent with the findings of the dornase alfa early intervention study<sup>23</sup> and the recent European data registry report.<sup>3</sup> The study was short term, and the results of a treatment order benefit beyond 2 weeks warrant additional investigation.

In summary, this study has demonstrated that dornase alfa is equally efficacious when delivered 30 minutes before or after physiotherapy. In selected patients who are persistently colonized with *P aeruginosa*, a better response may be elicited if dornase alfa is administered after physiotherapy.

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#### REFERENCES

- Desmond KJ, Schwenk WF, Thomas E, et al. Immediate and long term effects of chest physiotherapy in patients with cystic fibrosis. *J Pediatr*. 1983;103:538-542
- Frederickson B. Improved survival in the Danish centre-treated cystic fibrosis patients: results of aggressive treatment. *Pediatr Pulmonol*. 1996; 21:153-158
- Hodson ME, McKenzie S, Harms HK, et al. Dornase alfa in the treatment of cystic fibrosis in Europe: a report from the Epidemiologic Registry of Cystic Fibrosis. *Pediatr Pulmonol*. 2003;36:427-432
- Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med*. 1994;331:637-642
- Shak S. Aerosolized recombinant human DNase I for the treatment of cystic fibrosis. *Chest*. 1995;107:655-705
- Australasian Cystic Fibrosis Data Registry Annual Report 2004*. North Ryde, NSW, Australia: Cystic Fibrosis Australia; 2004
- Burrows JA, Bunting JP, Masel PJ, Bell SC. Nebulised dornase alfa: adherence in adults with cystic fibrosis. *J Cyst Fibros*. 2002;1:255-259
- Shwachman H, Kulczycki LL. Long term study of one hundred five patients with cystic fibrosis. *Am J Dis Child*. 1958;96:6-15
- American Thoracic Society. Standardization of spirometry—1994 Update. *Am J Crit Care Med*. 1995;152:1107-1136
- Polgar G, Promadhat V. *Pulmonary Function Testing in Children: Techniques and Standards*. Philadelphia, PA: WB Saunders Co; 1971
- Selvadurai HC, Cooper PJ, Meyers N, et al. Validation of shuttle tests in children with cystic fibrosis. *Pediatr Pulmonol*. 2003;35:133-138
- Orenstein D, Nixon PA, Ross EA, Kaplan RM. The quality of well-being in cystic fibrosis. *Chest*. 1989;95:344-347
- Eisenberg JD, Aitken ML, Dorkin HL, et al. Safety of repeated intermittent courses of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *J Pediatr*. 1997;131:118-124
- Hills M, Armitage P. The two-period cross-over clinical trial. *Br Med J Clin Pharmacol*. 1979;8:7-20
- Suri R, Metcalfe C, Wallis C, Bush A. Predicting response to rhDNase and hypertonic saline in children with cystic fibrosis. *Pediatr Pulmonol*. 2004;37:305-310
- Kettler LK, Sawyer SM, Winefield HR, Greville HW. Determinants of adherence in adults with cystic fibrosis. *Thorax*. 2002;57:459-464
- deMeer K, Gulmans VA, van der Laag J. Peripheral muscle weakness and exercise capacity in children with cystic fibrosis. *Am J Respir Crit Care Med*. 1999;159:748-754

18. Gulmans VAM, deMeer K, Brackel HJL, Faber JAJ, Berger R, Helders PJM. Outpatient exercise training in children with cystic fibrosis. *Pediatr Pulmonol.* 1999;28:39–46
19. Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programmes in children with cystic fibrosis. *Pediatr Pulmonol.* 2002; 33:194–200
20. Corey M, Farewell V. Determinants of mortality from cystic fibrosis in Canada. *Am J Epidemiol.* 1996;143:1007–1017
21. Fitzsimmons S. The changing epidemiology of cystic fibrosis. *J Pediatr.* 1993;122:1–9
22. Shak S, Capon DJ, Hellmiss R, Marsters SA, Baker CL. Recombinant DNase I reduces the viscosity of cystic fibrosis sputum. *Proc Natl Acad Sci U S A.* 1990;87:9188–9192
23. Quan JM, Tiddens HAWM, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr.* 2001;139: 813–820

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