Clinical Use of Dornase Alfa Is Associated With a Slower Rate of FEV_1 Decline in Cystic Fibrosis

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ONLINE SUPPLEMENT

Rate of Decline in FEV_1 in CF Patients Before and After an Arbitrary Time Point

Previous studies had evaluated the acute change in lung function after initiation of a new therapy, but in this study we wanted to evaluate the change in the rate of decline. A therapy that causes a lasting improvement in the rate of decline has the potential to greatly improve lung function for patients and may improve survival for cystic fibrosis (CF) patients.

In this supplement, we seek to explain what happens to the trajectory of lung function in CF patients unrelated to an acute event. Consider choosing an arbitrary point in time and assessing the lung function of a CF patient, as measured by forced expiratory volume in 1 second (FEV_1) % predicted, before and after that index time. At first thought, it may seem that there is no reason that the rate of decline would be any different before and after the arbitrary index time. However, Konstan et al (E1) have shown that among a number of risk factors for decline, high lung function is an independent risk factor. Therefore, patients with higher-than-average lung function are expected to experience a steeper-than-average decline going forward, and patients with lower lung function are expected to experience a less steep decline going forward. Furthermore, it stands to reason that patients with relatively high lung function at that index time are likely to have had more gradual prior decline than patients with relatively low lung function. (This is a sort of regression-to-the-mean effect looking backward in time.) These two factors combine to produce the expectation that patients with relatively high lung function at the index time are likely to show a change from mild decline to steeper decline, whereas those with relatively low lung function are likely to show a change from steep decline to milder decline. Thus, the null

hypothesis of no change in average decline before and after an arbitrary index time may need to be adjusted depending on the measured lung function at that index time.

In this supplement, we quantify the average rates of decline in FEV_1 % predicted before and after an index time, separately by disease stage, using spirometry data from all patients at least 6 years of age in the Epidemiologic Study of Cystic Fibrosis (ESCF), regardless of treatment. An index pulmonary function test (PFT) was defined as the PFT closest (within 30 days) to the first encounter within 1 year following the eighth or subsequent even-numbered birthday. (Even-numbered birthdays were used to avoid having overlapping pre-index periods.) The pre-index and post-index periods – each 2 years in duration – were each required to have ≥1 encounter and ≥3 FEV_1 values spanning at least 6 months to estimate the slope of FEV_1. Patients were included for as many sets of pre-index and post-index periods as they had available data.

When we characterized disease stage using FEV_1 % predicted values, we ran into the difficulty that there were few younger patients in the most severe categories and few older patients in the least severe categories. To provide for a more balanced distribution across categories by age, we characterized lung function relative to other CF patients at every age from 8 to 38 years using all PFTs in the ESCF (N = 535,344) to establish age-specific deciles of FEV_1 % predicted. Values defining the ten deciles by age are given in E-Table 1 and plotted in E-Figure 1.

For every patient and index value, separate regression lines were fit during each of the 2-year pre-index and post-index periods. The index PFT was used to establish the age-adjusted decile of severity but was excluded from both the pre-index and post-index periods to minimize issues

associated with regression to the mean. The regression lines were fit using PROC MIXED with 4 random effects: intercept (at the index PFT) and slope before the index event, and change in intercept and change in slope after the index event. (See Technical Note, below, for additional details.) Values for FEV_1 % predicted were calculated using the equations of Wang et al (E2) for males through age 17 years and for females through age 15 years and from the equations of Hankinson et al (E3) for older patients.

E-Figure 2 shows the average pre-index and post-index fitted lines by decile; E-Table 2 provides the details. In addition to estimating the average lines by decile, an overall estimate was obtained by combining the deciles using equal weighting (each decile counted equally) and the observed distribution (each decile counted according to the number of patients represented). These two ways of combining the deciles differ because the number of patients with available data varied by decile; the figure presents the version based on the observed distribution.

The results show the anticipated "bowing." The middle deciles have similar slope pre- and post-index with little change in intercept. For the lower deciles, the pre-index slopes are fairly steep compared to the post-index slopes, which are fairly flat. The opposite is the case for the higher deciles, where the pre-index slopes are fairly flat and the post-index slopes are fairly steep. The differences in estimated intercept are an indication that the straight lines do not adequately fit what is presumably a curved trajectory. Although it is reasonable to approximate the rate of change over short times using a straight line, fitting straight lines to up to 2 years of data may be more problematic. The more curved the true underlying trends, the more likely there is to be an observed difference in intercept when straight lines are fit.

A different way to look at these data is to examine the change in intercept and change in slope by decile. Change in intercept by FEV_1 decile is presented in E-Figure 3, which shows that some intercepts, especially at the highest deciles, are significantly different from zero, indicating a lack of fit in the model. Change in slope by FEV_1 decile is presented in E-Figure 4. This figure clearly shows the tendency for the trend line for the lowest deciles to flatten (change to a less negative slope) and for the trend line for the highest deciles to steepen (change to a more negative slope). For the lowest deciles (sickest patients), the slope improved by 2–3 points per year. For the highest deciles (healthiest patients), the slope worsened by 2–3 points.

The primary statistical model was unadjusted: it included time, the FEV_1 decile, and the interaction between decile and time. One concern was that part of the change in rate of decline over time might be due to the general tendency for patients to have more treatments over time. To address this and related questions, an adjusted model was estimated that included age and sex as fixed effects and various treatments as time-varying covariates. The estimated effect of the covariates and their associated standard errors were as follows: age (-1.72±0.01), female (-0.52±0.15), oral antibiotics (-0.76±0.03), inhaled antibiotics (0.08±0.03), oral bronchodilators (-0.31±0.08), inhaled bronchodilators (-0.51±0.05), oral corticosteroids (-1.89±0.05), inhaled corticosteroids (0.05±0.04), mast cell stabilizers (0.08±0.06), oral supplements (-0.21±0.04), enteral supplements (-1.79±0.08), parenteral supplements (-1.98±0.20), and pulmonary exacerbations treated with IV antibiotics (-2.11±0.04 any since previous PFT; 2.08±0.04 within 28 days before the PFT; -5.42±0.04 within 28 days after the PFT). The results were remarkably similar to those for the unadjusted model (data not shown).

These results clearly show that the null hypothesis of no change in slope in FEV_1 % predicted is not appropriate for patients with low or high lung function relative to their peers. It provides some quantitative guidance about the magnitude of the expected change in slope looking before and after an arbitrary index time based on age-adjusted decile of FEV_1 % predicted.

Technical Note

In the mixed model, the pre-index slope, intercept (at the index date) of the pre-index line, difference in slope (post-index minus pre-index), and difference in intercept (post-index minus pre-index) were treated as random effects at the patient-index point level. To fully account for the repeated use of patients, variance components would be estimated at the patient level for all 4 parameters, but we found that the patient-level parameters corresponding to difference in slope and difference in intercept were near zero and so were dropped. This means that we effectively assumed that the variability in amount of *change* in slope and *change* in intercept within patients was similar to the variability between patients. In contrast, the overall slope and intercept were more similar within patients than between patients, so those variance components were retained in the model.

The model code includes the following statements within PROC MIXED:

```
class patid patid_age decile;
model fev1pct = decile decile*t decile*t0 decile*tafter
                [list of covariates] / solution ddfm=bw;
random intercept t / sub=patid type=fa0(2) g gcorr;
random intercept t t0 tafter / sub=patid_age(patid) type=fa0(4) g gcorr;
```

The variable t represents time in years ranging from -2 to +2 where 0 represents the index PFT. The variable t0=max(t,0) and is therefore 0 for $t \leq 0$ and equal to t thereafter; this represents the

change in slope. The indicator variable tafter is 1 if t>0 and 0 otherwise and represents the change in intercept.

E-References

E1. Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, Stokes DC, Wohl ME, Wagener JS, Regelmann WE, Johnson CA. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. J Pediatr 2007;151:134–139.

E2. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15:75–88.

E3. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–187.

E-Fig. 1. FEV_1 % predicted decile by age at PFT for all patients enrolled in the ESCF.

E-Fig. 2. Pre- and post-index slopes and increment at index event by FEV_1 decile – unadjusted model.

E-Fig. 3. Change in intercept by FEV_1 decile – unadjusted model (error bars represent 95% confidence interval).

E-Fig. 4. Change in slope by FEV_1 decile*– unadjusted model (error bars represent 95% confidence interval).

E-TABLE 1—FEV_1 % Predicted ~~Decile*~~ 10th to 90th Percentiles by Age for All Patients Enrolled in the ESCF

Age	10th %ile	20th %ile	30th %ile	40th %ile	50th %ile	60th %ile	70th %ile	80th %ile	90th %ile
8	50.5	64.2	73.6	81.1	87.3	92.7	98.1	103.6	111.2
9	48.0	62.3	72.3	79.7	86.1	91.7	97.0	102.9	110.7
10	47.7	61.1	71.0	79.0	85.4	91.0	96.4	102.2	109.8
11	46.2	60.0	69.8	77.5	84.0	89.8	95.4	101.3	109.0
12	42.4	55.5	65.8	74.0	81.2	87.4	93.4	99.9	107.9
13	40.2	52.5	62.9	71.3	78.4	84.8	91.3	97.9	106.4
14	37.7	49.7	59.8	68.0	75.4	82.1	88.8	95.8	104.5
15	35.2	46.2	55.8	64.2	71.8	78.9	85.6	93.0	102.0
16	32.9	43.3	52.3	60.2	67.5	74.5	81.4	89.0	98.4
17	31.2	40.4	49.1	56.8	64.1	71.1	78.3	86.1	95.6
18	29.1	38.0	46.2	53.7	61.0	68.3	75.5	83.3	93.1
19	27.8	35.7	43.0	50.3	57.7	64.7	72.1	80.5	90.9
20	25.9	33.3	40.1	47.1	54.4	61.6	69.2	77.9	88.2
21	26.5	33.6	40.3	47.0	53.7	61.0	68.6	76.7	86.9
22	26.2	32.6	38.8	45.3	52.3	59.4	66.6	75.2	86.1
23	25.6	32.2	38.1	44.6	51.2	57.9	65.1	74.1	85.5
24	24.6	30.9	36.5	42.9	49.4	56.0	63.1	72.2	84.2
25	24.1	30.1	35.5	41.7	48.2	54.7	62.3	71.1	83.5
26	23.2	28.7	33.8	39.7	46.3	53.2	61.1	69.9	83.0
27	23.0	28.2	33.2	39.1	45.4	52.1	59.7	69.1	81.6
28	22.7	28.1	33.1	38.4	45.0	51.8	59.2	68.1	80.1
29	22.2	27.7	32.6	38.1	44.2	50.8	58.6	67.4	78.6
30	22.6	28.1	33.1	38.1	43.8	50.0	57.8	66.2	77.6
31	22.5	27.3	32.2	37.5	43.1	49.1	56.0	64.7	77.5
32	22.5	27.2	32.0	36.9	42.4	48.8	56.0	64.1	76.9
33	22.4	27.0	31.5	37.6	43.0	48.8	55.3	64.6	75.8
34	21.9	26.3	31.3	36.7	42.4	48.4	55.6	64.5	76.7
35	21.2	25.9	30.4	34.6	40.7	47.4	54.4	63.6	76.2
36	21.4	26.8	31.2	35.7	41.2	47.2	54.8	63.8	76.3
37	22.0	27.2	32.1	36.6	41.8	46.7	53.8	63.3	75.4
38	21.7	27.1	32.4	37.2	42.3	47.7	54.1	63.0	75.7

E-TABLE 2—Unadjusted* Annual Slope and Intercept for FEV_1 % Predicted† Pre- and Post-Index Event

	N	Pre-index slope (SE)	Post-index slope (SE)	Slope difference (SE)	*P* difference	Post-index increase (SE)	*P* increase	Pre-index start	Pre-index stop	Post-index start	Post-index Stop
Combined (observed)	32355	–1.38 (0.05)	–1.98 (0.04)	–0.60 (0.06)	<0.001	–0.40 (0.06)	<0.001	75.61	72.85	72.45	68.50
Combined (uniform)	32355	–1.60 (0.05)	–1.92 (0.04)	–0.31 (0.06)	<0.001	–0.36 (0.06)	<0.001	73.91	70.70	70.33	66.50
1	2155	–4.05 (0.16)	–1.07 (0.16)	2.97 (0.23)	<0.001	0.00 (0.21)	1.00	54.74	46.65	46.65	44.50
2	2511	–3.29 (0.15)	–1.56 (0.15)	1.73 (0.21)	<0.001	0.01 (0.20)	0.95	61.53	54.95	54.96	51.84
3	2874	–2.33 (0.15)	–1.86 (0.14)	0.47 (0.20)	0.021	–0.47 (0.19)	0.014	65.97	61.32	60.85	57.12
4	3091	–2.35 (0.14)	–1.97 (0.13)	0.38 (0.20)	0.057	–0.10 (0.19)	0.59	70.57	65.88	65.78	61.85
5	3292	–1.87 (0.14)	–2.00 (0.13)	–0.13 (0.20)	0.52	–0.14 (0.19)	0.46	73.95	70.21	70.07	66.08
6	3428	–1.30 (0.14)	–1.82 (0.13)	–0.52 (0.19)	0.007	–0.58 (0.19)	0.002	76.49	73.90	73.32	69.68
7	3639	–0.90 (0.14)	–1.90 (0.13)	–1.00 (0.19)	<0.001	–0.36 (0.19)	0.059	78.76	76.96	76.60	72.81
8	3768	–0.43 (0.14)	–2.20 (0.13)	–1.77 (0.19)	<0.001	–0.69 (0.19)	<0.001	81.97	81.12	80.43	76.03
9	3782	–0.02 (0.14)	–2.03 (0.13)	–2.01 (0.19)	<0.001	–0.92 (0.19)	<0.001	85.13	85.08	84.16	80.10
10	3815	0.49 (0.14)	–2.77 (0.14)	–3.26 (0.20)	<0.001	–0.40 (0.20)	0.040	89.94	90.92	90.51	84.98

*Covariate include disease stage interacted with time.
†FEV_1 % predicted is calculated based on Wang and Hankinson algorithms.

E-TABLE 1—FEV_1 % Predicted 10^{th} to 90^{th} Percentiles by Age for All Patients Enrolled in the ESCF

Age	10^{th} %ile	20^{th} %ile	30^{th} %ile	40^{th} %ile	50^{th} %ile	60^{th} %ile	70^{th} %ile	80^{th} %ile	90^{th} %ile
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32	22.5	27.2	32.0	36.9	42.4	48.8	56.0	64.1	76.9
33	22.4	27.0	31.5	37.6	43.0	48.8	55.3	64.6	75.8
34	21.9	26.3	31.3	36.7	42.4	48.4	55.6	64.5	76.7
35	21.2	25.9	30.4	34.6	40.7	47.4	54.4	63.6	76.2
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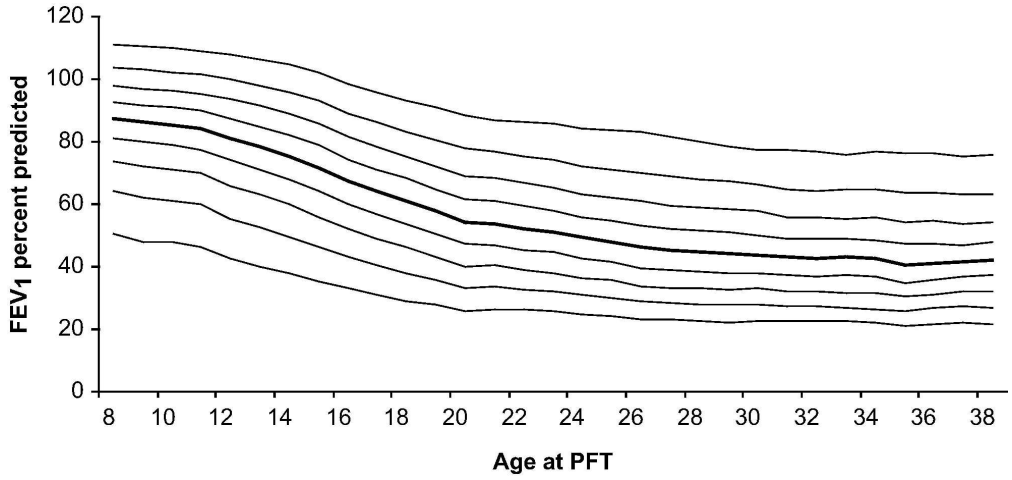
*Covariate include disease stage interacted with time.

†FEV_1 % predicted is calculated based on Wang and Hankinson algorithms.



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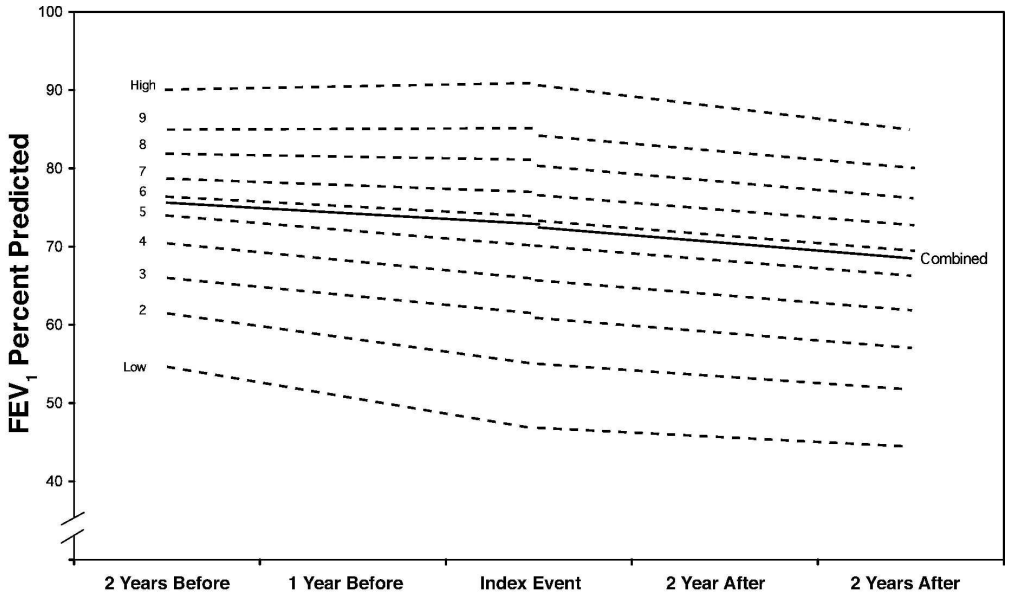

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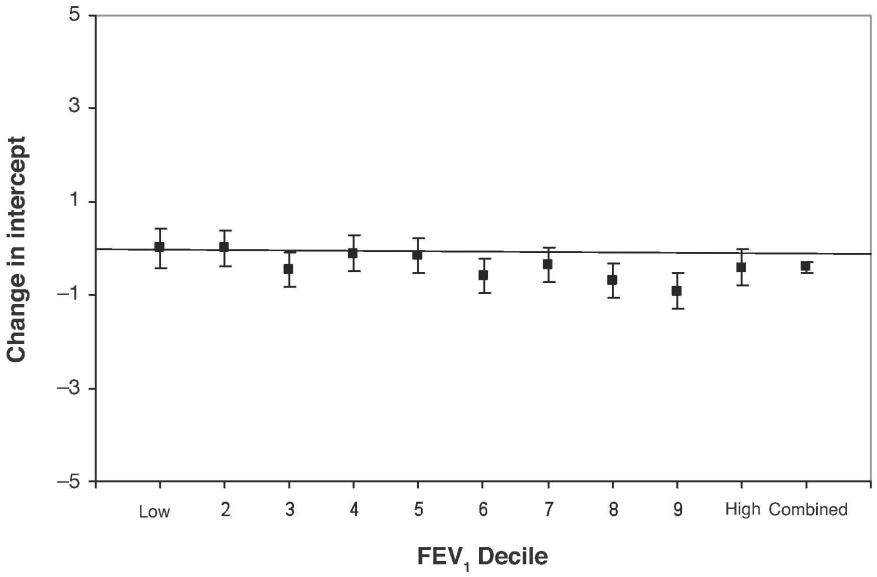

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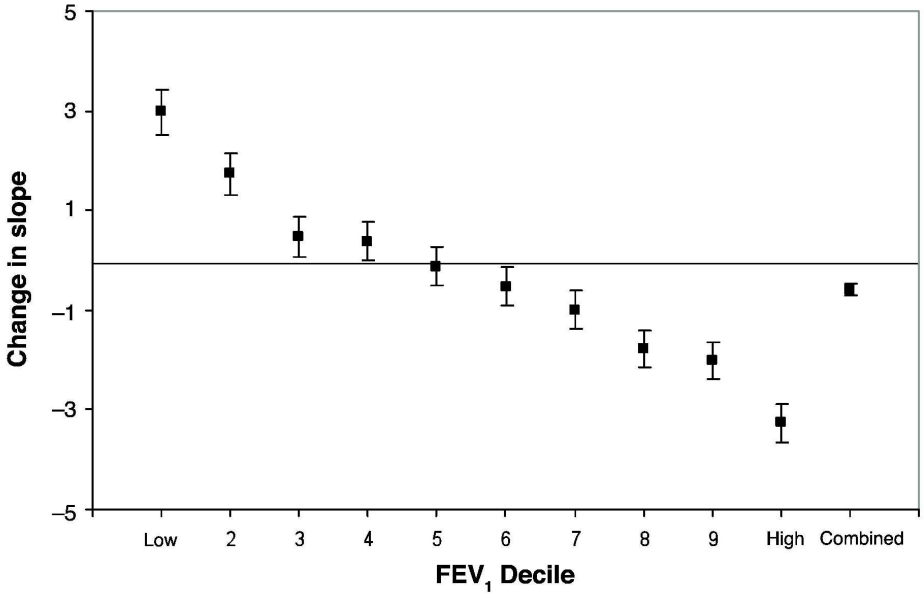

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