

# A first-year dornase alfa treatment impact on clinical parameters of patients with cystic fibrosis: the Brazilian cystic fibrosis multicenter study

*O impacto de primeiro ano de tratamento com dornase alfa nos parâmetros clínicos de pacientes com fibrose cística: estudo multicêntrico brasileiro*

*El impacto de primer año de tratamiento con dornasa alfa en los parámetros clínicos de pacientes con fibrosis quística: resultado de estudio brasileño multicéntrico*

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## ABSTRACT

**Objective:** To describe the clinical impact of the first year treatment with dornase alfa, according to age groups, in a cohort of Brazilian Cystic Fibrosis (CF) patients.

**Methods:** The data on 152 eligible patients, from 16 CF reference centers, that answered the medical questionnaires and performed laboratory tests at baseline (T0), and at six (T2) and 12 (T4) months after dornase alfa initiation, were analyzed. Three age groups were assessed: six to 11, 12 to 13, and  $\geq 14$  years. Pulmonary tests, airway microbiology, emergency room visits, hospitalizations, emergency and routine treatments were evaluated. Student's *t*-test, chi-square test and analysis of variance were used when appropriated.

**Results:** Routine treatments were based on respiratory physical therapy, regular exercises, pancreatic enzymes, vitamins, bronchodilators, corticosteroids, and antibiotics. In the six months prior the study (T0 phase), hospitalizations for pulmonary exacerbations occurred in 38.0, 10.0 and 61.4% in the three age groups, respectively. After one year of

intervention, there was a significant reduction in the number of emergency room visits in the six to 11 years group. There were no significant changes in forced expiratory volume in one second (VEF<sub>1</sub>), in forced vital capacity (FVC), in oxygen saturation (SpO<sub>2</sub>), and in Tiffenau index for all age groups. A significant improvement in Shwachman-Kulczychi score was observed in the older group. In the last six months of therapy, chronic or intermittent colonization by *P. aeruginosa* was detected in 75.0, 71.4 and 62.5% of the studied groups, respectively, while *S. aureus* colonization was identified in 68.6, 66.6 and 41.9% of the cases.

**Conclusions:** The treatment with dornase alfa promoted the maintenance of pulmonary function parameters and was associated with a significant reduction of emergency room visits due to pulmonary exacerbations in the six to 11 years age group, with better clinical scores in the  $\geq 14$  age group, one year after the intervention.

**Key-words:** cystic fibrosis; dornase alfa; therapeutics; clinical evolution; pulmonary microbiology.

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Fonte financiadora: Produtos Roche do Brasil. A indústria, ao fim do estudo, doou equipamentos médicos e/ou computadores a cada Centro de Fibrose Cística. O monitoramento dos Centros, quando necessário, foi feito pela pesquisadora principal e por uma monitora, com facilidades de transporte e eventuais gastos durante as viagens custeados pela Produtos Roche. O custo da análise estatística, realizada por firma independente, foi arcado pela indústria. Conflito de interesse: a indústria não interferiu no desenho do estudo, na análise e na discussão dos dados.

Recebido em: 22/11/2012

Aprovado em: 15/5/2013

## RESUMO

**Objetivo:** Relatar o impacto clínico do primeiro ano de tratamento com dornase alfa de acordo com a faixa etária, numa coorte de pacientes brasileiros com fibrose cística (FC).

**Métodos:** O presente estudo analisou dados de 152 pacientes elegíveis, de 16 centros de referência para FC, os quais responderam aos questionários clínicos e realizaram testes laboratoriais, ao início do tratamento com dornase alfa (T0) e após seis (T2) e 12 (T4) meses da intervenção. Analisaram-se três grupos etários: seis a 11, 12 a 13 e  $\geq 14$  anos de idade. Avaliaram-se os testes pulmonares, a microbiologia de vias aéreas, os atendimentos de emergência, as hospitalizações e os tratamentos emergenciais e rotineiros. O teste *t* de Student, o qui-quadrado e a análise de variância foram usados quando pertinentes.

**Resultados:** O tratamento baseou-se em fisioterapia respiratória, exercícios regulares, enzimas pancreáticas, vitaminas, broncodilatadores, corticosteroides e antibióticos. Nos seis meses anteriores ao estudo (fase T0), as hospitalizações por exacerbação pulmonar ocorreram em 38,0, 10,0 e 61,4%, respectivamente para as três faixas etárias analisadas. No grupo de seis a 11 anos, houve redução significativa de atendimentos de emergência após um ano de tratamento. Não houve modificações significativas de volume expiratório forçado no primeiro segundo (VEF<sub>1</sub>), capacidade vital forçada (CVF), saturação de oxigênio (SpO<sub>2</sub>) e índice de Tiffeneau em todos os grupos. O escore de Shwachman-Kulczycki melhorou significativamente no grupo de mais idade. Nos últimos seis meses de tratamento, a colonização crônica ou intermitente por *P.aeruginosa* foi detectada em 75,0, 71,4 e 62,5%, respectivamente, enquanto a colonização por *S.aureus* ocorreu em 68,6, 66,6 e 41,9% dos casos em cada grupo etário.

**Conclusões:** A intervenção com dornase alfa resultou em manutenção dos parâmetros pulmonares e associou-se à redução significativa de visitas à emergência por exacerbação pulmonar no grupo de seis a 11 anos de idade, com melhora do escore clínico no grupo  $\geq 14$  anos de idade ao final de um ano de estudo.

**Palavras-chave:** fibrose cística; dornase alfa; terapêutica; evolução clínica; microbiologia pulmonar.

## RESUMEN

**Objetivo:** Relatar el impacto clínico del primer año de tratamiento con dornase alfa conforme a la franja de edad, en una cohorte de pacientes brasileños con fibrosis quística (FC).

**Métodos:** El presente estudio analizó datos de 152 pacientes elegibles, de 16 centros de referencia para FC, los que contestaron a los cuestionarios clínicos y realizaron pruebas laboratoriales, al inicio del tratamiento con la dornasa alfa (T0) y después de 6 (T2) y 12 (T4) meses de la intervención. Se analizaron 3 grupos etarios: 6–11, 12–13 e  $> 14$  años de edad. Se evaluaron las pruebas pulmonares, la microbiología de vías aéreas, las atenciones de emergencia, hospitalizaciones y tratamientos emergenciales y de rutina. Las estadísticas descriptivas, pruebas *t* y chi-cuadrado y ANOVA fueron usadas cuando pertinentes.

**Resultados:** El tratamiento regular se basó en la fisioterapia respiratoria, ejercicios regulares, encimas pancreáticas, vitaminas, broncodilatadores, corticosteroides y antibióticos. En los 6 meses anteriores al estudio (fase T0), las hospitalizaciones por exacerbação pulmonar ocurrieron en 38, 10 y 61,4%, respectivamente, para las tres franjas de edad analizadas. En el grupo 6–11 años, hubo reducción significativa de atenciones de emergencia después de 1 año de tratamiento. No hubo modificaciones significativas de volumen espiratorio forzado en el 1er segundo (VEF<sub>1</sub>), capacidad vital forzada (CVF), saturación de oxígeno (SpO<sub>2</sub>) e índice de Tiffeneau, en todos grupos. El escore de Schwachman-Kulczycki mejoró significativamente en el grupo de más edad. Los últimos 6 meses de tratamiento, la colonización crónica o intermitente por *P. aeruginosa* fue detectada en el 75, 71,4 y 62,5%, respectivamente, mientras que por *S. aureus* ocurrió en 68,6, 66,6 y 41,9% de los casos en cada grupo de edad.

**Conclusiones:** La intervención con dornasa alfa resultó en mantenimiento de los parámetros pulmonares y fue asociada a la reducción significativa de visitas a la emergencia por exacerbação pulmonar en el grupo de 6 a 11 años de edad, con mejora del escore clínico en el grupo  $\geq 14$  años de edad, al final de un año de estudio.

**Palabras clave:** fibrosis quística; dornasa alfa; tratamiento; evolución clínica; microbiología pulmonar.

## Introduction

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disorder among Caucasians<sup>(1,2)</sup>. Caused by a mutation in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene, this disease is characterized by progressive lung destruction, with accumulation of viscous secretions and impairment of mucociliary clearance in airways<sup>(3,4)</sup>. Chronic pulmonary infection and increased inflammatory

response are hallmarks of CF lung disease, with a major impact on patients' morbidity and the mortality<sup>(4-6)</sup>.

Long-term accumulation of thickened mucus leads to chronic suppurative lung disease, with persistent infection or colonization by microorganisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Burkholderia cepacia*, and evolution to bronchiectasis, pneumothorax, *cor pulmonale*, and respiratory failure, at the final stage of disease<sup>(7)</sup>. Gastrointestinal and reproductive systems are also affected with pancreatic insufficiency with maldigestion and malabsorption of nutrients, distal intestinal obstruction, and hepatic disease. In addition, salt loss syndromes, *diabetes mellitus*, and genitourinary abnormalities are other clinical complications of CF<sup>(2,8)</sup>.

Improvements in CF diagnosis and treatment strategies led to an increase in life expectancy, raising the median age of survival to 36 years in the United States<sup>1</sup> and around 18 years in Brazil<sup>(9)</sup>. Although no cure exists, several therapeutic strategies are available for clinical use and current standard treatments for CF include antibiotics, respiratory physical therapy and mucolytic agents (dornase alfa, hypertonic saline solutions), bronchodilators, pancreatic enzymes, and daily supplementation with vitamins<sup>(5,8,10)</sup>.

Clinical use of dornase alfa, a recombinant human deoxyribonuclease I that reduces the viscosity of CF sputum through the hydrolyzation of DNA accumulated in secretions<sup>(11)</sup>, has demonstrated significant efficacy in CF, as it reduces respiratory exacerbations and improves lung function, regardless of patients age or disease stage<sup>(5,12,13)</sup>.

Health-related quality of life (HRQoL) has gained importance lately as an endpoint for clinical trials, so we have conducted a multicenter prospective study to investigate the impact of dornase alfa introduction on patients' QoL. In our previous publication<sup>(14)</sup> we used modified, Portuguese-translated, validated CF QoL questionnaires CFQ-R (Cystic Fibrosis Questionnaire-Revised)<sup>(15)</sup>, with dornase alfa promoting significant improvements in various CFQ-R domains. The aim of this publication is to present additional information about the clinical profile of CF Brazilian patients after starting dornase alfa chronic use and to analyze their clinical parameters and patterns of care.

## Method

This paper shows complementary data of the 152 CF patients from the Brazilian Cystic Fibrosis Quality of Life Trial<sup>(14)</sup>. Study design, sample size, patient eligibility criteria, and part

of patients' demographic and clinical characteristics have been described previously<sup>(14)</sup>. Free informed consent form was signed by patients or their guardians and this project was approved by human research ethics committees of all Centers<sup>(14)</sup>.

Patients were followed in five outpatient visits: previous to dornase alfa initiation (T0), and then every 3 months until one year of follow up — 3 (T1), 6 (T2), 9 (T3) and 12 (T4) months, respectively. In all visits, disease-specific questionnaires, CFQ-R translated and validated, were used in patients aged from 6 to 11, 12 to 13 and 14 years or more, and in parents of patients aged 6 to 13 years<sup>(15,16)</sup>. The responsible physician evaluated patient's medical record forms covering the last six months, prior to study entry (T0), and at 6 months (T2) and 12 months (T4) of dornase alfa. For each patient, these three forms and the following parameters were collected: method of CF diagnosis; reason, number and duration of hospitalizations; reason and number of visits to the emergency room; concomitant interventions routinely used; pulmonary function parameters forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital capacity [FVC], oxygen saturation of hemoglobin [SpO<sub>2</sub>] and Tiffeneau index; Shwachman-Kulczycki score; treatments for pulmonary exacerbations; use of antibiotics and airways microbiology. Patient condition/evolution and reason for follow-up interruption were obtained after 6 and 12 months. In addition, a clinical stability questionnaire was used to evaluate the clinical conditions in the previous month<sup>(14)</sup>.

Genetic studies were performed by specific polymerase chain reaction. At each visit, physical examination, laboratory measures, and a spirometry were performed. Sputum cultures were collected routinely and considered positive when the following microorganisms were presented in at least one sample: *S. aureus*; *P. aeruginosa*; *B. cepacia* or *Stenotrophomonas maltophilia*. The colonization was defined as chronic when 3 positive samples were obtained, in previous 6 months.

The following variables were analyzed: age, gender, symptoms, diagnosis, medication use, pulmonary function parameters, concomitant treatments, and airway microbiology. Clinical outcomes and data on concomitant treatments, medication use, and routine therapies were based on data recorded.

Patients were analyzed according to the age-groups<sup>(14,16)</sup>. Data were summarized using descriptive statistics suitable for each variable. Frequency and percentages were used for categorical variables and for ordinal numerical variables. Number of valid observations, range, mean, standard deviation (SD), median, and interquartile range were used to

describe continuous numerical variables, including FEV<sub>1</sub>, FVC, SpO<sub>2</sub>, Tiffeneau index, and Shwachman-Kulczycki score. Values for percentage of predicted FEV<sub>1</sub> and FVC were calculated. Parametric data were compared between two groups using t-test for paired samples, when appropriated. Comparison between three or more means was performed using the analysis of variance. Changes in FEV<sub>1</sub>, FVC, SpO<sub>2</sub>, Tiffeneau index and Shwachman-Kulczycki score were assessed using the analysis of variance for repeated measures and multiple comparisons. The number of visits to the emergency room due to acute pulmonary exacerbations was compared over time using the McNemar test for dependent samples, and using Chi-square test for independent samples. Statistical analyses were performed using the SAS software (SAS Institute Inc). Two-sided  $p < 0.05$  were considered statistically significant.

Sample size calculation was performed as previously described and based on the primary *endpoint* of the study which was the quality of life<sup>(14)</sup>. Briefly, based on the variance analysis of the CFQ-R punctuation found in a previous study<sup>(15)</sup> it was estimated that the inclusion of 64 patients per age group would give the study a power of 80% to detect a variation of 6.5% in the Respiratory Symptoms domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) based on a two-sided type I error  $\leq 5\%$ .

## Results

Of the 156 initial patients, four were excluded for not meeting the inclusion criteria. Among the 152 eligible patients, 79 were in age group 6–11, 14 were in age group 12–13, and 59 were in age group  $\geq 14$  years, from 16 CF referral centers. Overall and

**Table 1** - Outpatient clinic and emergency room visits, hospitalizations, and pulmonary function parameters in the last 6 months prior to the study entry, and at 6 and 12 months after dornase alfa initiation in patients aged 6–11 years. Part of these results was previously published<sup>(14)</sup>

	T0	T2	T4	p-value
Visits to the emergency room	23/77 (29.9%)	9/67 (13.4%)	13/60 (21.7%)	0.060
Visits to the emergency room due to acute exacerbations*	13/23 (56.5%)	4/9 (44.4%)	2/13 (15.4%)	0.056
Hospitalization due to acute exacerbations	14/77 (18.2%)	7/67 (10.4%)	5/60 (8.3%)	0.181
Visits to outpatient clinic due to acute exacerbations	37/77 (48.1%)	31/67 (46.3%)	25/60 (41.7%)	0.751
FEV <sub>1</sub> (% predicted)**	<i>n</i> =61	<i>n</i> =55	<i>n</i> =52	
Mean±SD	79.5±21.1	81.3±22.0	83.4±21.7	0.411
Median (range)	79.0 (29.0–115.0)	80.0 (14.0–147.0)	84.0 (44.0–132.0)	
FVC (% predicted)**	<i>n</i> =61	<i>n</i> =54	<i>n</i> =52	
Mean±SD	86.7±19.7	88.5±18.0	89.4±20.0	
Median (range)	87.0 (47.0–131.0)	91.5 (49.0–135.0)	92.5 (50.0–149.0)	0.580
SpO <sub>2</sub> **	<i>n</i> =51	<i>n</i> =49	<i>n</i> =43	
Mean±SD	96.0±2.3	95.6±7.0	97.0±2.1	0.227
Median (range)	96.0 (89.0–99.0)	97.0 (58.0–100.0)	97.0 (88.0–100.0)	
Tiffeneau index**	<i>n</i> =60	<i>n</i> =56	<i>n</i> =51	
Mean±SD	85.9±15.9	88.3±11.7	86.2±13.3	
Median (range)	89.0 (33.0–116.6)	89.0 (43.0–110.0)	86.0 (50.0–109.5)	0.551
Shwachman-Kulczycki score**	<i>n</i> =72	<i>n</i> =58	<i>n</i> =50	
Mean±SD	80.7±12.2	83.0±11.8	83.1±12.0	
Median (range)	80.0 (55.0–100.0)	85.0 (55.0–100.0)	85.0 (52.0–100.0)	0.268

\*McNemar test (dependent times): T0=T2; T0=T4 e T2=T4; Fisher exact test (independent times): T0=T2; T0>T4 e T2=T4; \*\**p*-values were calculated using repeated measures analysis of variance; T0: baseline visit; T2: visit at 6 months of dornase alfa; T4: visit at 12 months of dornase alfa; FVC: forced vital capacity; SpO<sub>2</sub>: oxygen saturation; SD: standard deviation; VEF<sub>1</sub>: forced expiratory volume in 1 second

per age group descriptive analysis of gender, age, age at diagnosis, and clinical manifestations were previously described<sup>(14)</sup>. During the follow-up, 14 patients were lost for the following reasons: withdrawal from the treatment (4), death (3), frequently missed visits (1), transference to another city/state (1), pregnancy (1), lack of medication at the distribution site (1), drug intolerance (1), low adherence (1) and adverse reaction n(1).

The main method of CF diagnosis was based on two sweat tests associated or not to genetic studies. In the younger group, ΔF508 in homozygotic state was the most frequent mutation (42.9%), followed by ΔF508 in heterozygosis (32.1%) and unknown mutations (14.3%). In patients aged ≥14 years, the most common mutations were ΔF508 in heterozygosis (31.3%), ΔF508 in homozygosis (18.8%) and unknown mutations (37.5%). Other mutations, E542X/B10665, G542X/N1303K, R1162X/R1162, W1282X/N, and ΔF508/R553X, were detected.

Pulmonary function parameters and data related to hospitalization are presented in Tables 1 to 3.

Data on patients aged from 6 to 11 years are summarized in Table 1. During the study, patients in this group required

hospitalizations; most cases lasted from 11 to 20 days and were predominantly due to pulmonary infections. There was a significant reduction in the number of emergency room visits due to acute exacerbations when T4 was compared to T0. This age group showed no significant changes in FEV<sub>1</sub>, FVC, SpO<sub>2</sub>, Tiffeneau index and Shwachman-Kulczychi score after 6 and 12 months of dornase alfa.

Regarding the age group 12–13 years, pulmonary function parameters are summarized in Table 2. Due to sample size limitations, no statistical comparisons were made for this group regarding outcomes over time.

For the group aged ≥14 years, 16 patients were hospitalized due to pulmonary infections, with a length of stay that varied from 10 to 20 days. There were many visits to emergency rooms. When time points T0–T4 were compared, no significant differences were observed regarding the number of visits due to acute exacerbations. In addition, treatment with dornase alfa for 6 and 12 months was not associated with significant changes in pulmonary function parameters, with the exception of Shwachman-Kulczychi score that showed a significant improvement after 6 months of dornase alfa (Table 3).

**Table 2** - Outpatient clinic and emergency room visits, hospitalizations and pulmonary function parameters in the last 6 months prior to study entry, at 6 and 12 months after dornase alfa initiation in patients aged 12-13 years. Part of these results was previously published<sup>(14)</sup>

	T0	T2	T4
Visits to the emergency room	2/13 (15.4%)	4/11 (36.4%)	0/10 (0.0%)
Hospitalization due to acute exacerbations	1/13 (7.7%)	3/11 (27.3%)	1/10 (10.0%)
Visits to outpatient clinic due to acute exacerbations	3/13 (23.1%)	3/11 (27.3%)	4/10 (40.0%)
FEV <sub>1</sub> (% predicted)	n=12	n=9	n=9
Mean±SD	68.6±15.2	67.4±16.1	67.0±17.2
Median (range)	69.0 (42.0–94.0)	66.0 (42.0–99.7)	61.3 (44.0–99.0)
FVC(% predicted)	n=12	n=9	n=9
Mean±SD	80.7±16.4	80.1±14.8	81.7±16.9
Median (range)	75.7(52.7–114.1)	72.0(67.0–102.0)	75.0(60.0–107.3)
SpO <sub>2</sub>	n=10	n=8	n=7
Mean±SD	96.7±1.9	96.8±1.3	96.3±2.8
Median (range)	97.0 (93.0–99.0)	97.0 (95.0–98.0)	97.0 (91.0–99.0)
Tiffeneau index	n=12	n=10	n=8
Mean±SD	81.2±10.9	83.5±12.5	83.8±11.5
Median (range)	82.0 (63.0–103.0)	83.0 (63.0–103.1)	87.5 (66.0–98.0)
Shwachman-Kulczychi score	n=12	n=7	n=8
Mean±SD	75.2±13.3	77.4±15.5	81.1±10.9
Median (range)	75.0 (55.0–97.0)	80.0 (50.0–97.0)	84.0 (60.0–95.0)

T0: baseline visit; T2: visit at 6 months of dornase alfa; T4: visit at 12 months of dornase alfa; FVC: forced vital capacity; SpO<sub>2</sub>: oxygen saturation; SD: standard deviation; VEF<sub>1</sub>: forced expiratory volume in 1 second

Analysis of airways microbiology is shown in Table 4. In all age groups, *P. aeruginosa* and *S. aureus* were the most frequent pathogens found in chronic and intermittent colonization. During the first six months of dornase alfa, chronic *P. aeruginosa* was detected in 37.9%, 37.5% and 47.4% of the patients in age groups 6-11, 12-13 and  $\geq 14$  years, respectively, while chronic *S. aureus* was identified in 20.0%, 44.4% and 22.5% of the patients. When chronic and intermittent colonization were grouped, *P. aeruginosa* was found in more than 60% of the sample during treatment with dornase alfa, while *S. aureus* colonization showed a prevalence higher than 40-60%, for all age groups.

The routine concomitant treatments during the study follow-up are shown in Table 5.

The missing data has many reasons as incompletely fulfilled documents, patients' faults to clinics, physician

misunderstanding of proposed questions, and CF younger patients lack of cooperation during pulmonary tests.

## Discussion

We described the clinical characteristics and outcomes of the 152 patients included in the Brazilian Cystic Fibrosis Quality of Life Trial<sup>(14)</sup>. The selection of CF patients in the 16 referral centers was based on the physicians' decision to initiate chronic treatment with dornase alfa, following the recommendations of current consensus<sup>(1,5)</sup>, with no additional costs to the routine treatment, as this medication is regularly dispensed by our government. According to the international guidelines, the chronic use of dornase alfa, aiming at improving lung function and reducing exacerbations in children with 6 years of age and older in moderate to severe

**Table 3** - Outpatient clinic and emergency room visits, hospitalizations and pulmonary function parameters in the last 6 months prior to the study entry, at 6 and 12 months after dornase alfa initiation in patients aged  $\geq 14$  years. Part of these results was previously published<sup>(14)</sup>

	T0	T2	T4	p-value
Visits to the emergency room	20/74 (27.0%)	13/49 (26.5%)	8/38 (21.1%)	0.443
Visits to the emergency room due to acute exacerbations	11/19 (57.9%)	6/13 (46.2%)	7/8 (87.5%)	0.166
Hospitalization due to acute exacerbations*	21/59 (35.6%)	8/49 (16.3%)	5/38 (13.2%)	0.014
Visits to outpatient clinic due to acute exacerbations	35/59 (59.3%)	24/49 (49.0%)	13/38 (34.2%)	0.054
FEV <sub>1</sub> (% predicted)	n=52	n=47	n=35	
Mean $\pm$ SD	65.1 $\pm$ 22.7	64.6 $\pm$ 23.5	67.1 $\pm$ 22.3	
Median (range)	70.4 (17.0–115.0)	68.6 (14.0–118.0)	70.0 (25.0–119.0)	0.864
FVC(% predicted)	n=51	n=47	n=35	
Mean $\pm$ SD	74.5 $\pm$ 21.6	75.9 $\pm$ 22.0	77.8 $\pm$ 21.5	
Median (range)	78.0 (24.0–121.0)	78.1 (19.0–118.0)	77.0 (32.6–125.0)	0.603
SpO <sub>2</sub>	n=44	n=42	n=32	
Mean $\pm$ SD	95.4 $\pm$ 3.6	95.6 $\pm$ 2.9	95.8 $\pm$ 2.2	0.924
Median (range)	96.0 (78.0–100.0)	96.0 (86.0–100.0)	96.0 (89.0–100.0)	
Tiffeneau index	n=54	n=45	n=36	
Mean $\pm$ SD	76.2 $\pm$ 15.7	74.9 $\pm$ 15.7	78.9 $\pm$ 15.8	0.160
Median (range)	78.2 (37.0–109.0)	73.0 (42.0–101.0)	80.5 (41.6–103.0)	
Shwachman-Kulczycki score**	n=39	n=31	n=24	
Mean $\pm$ SD	75.2 $\pm$ 15.2	79.3 $\pm$ 12.1	79.2 $\pm$ 12.6	0.046*
Median (range)	80.0 (45.0–100.0)	80.0 (50.0–99.0)	80.0 (50.0–95.0)	

\*McNemar test (dependent times) and Chi-square (independent times): T0<>T2; T0<>T4 and T2=T4; \*\*T0<T2, T0=T4, T2=T4; T0: baseline visit; T2: visit at 6 months of dornase alfa; T4: visit at 12 months of dornase alfa; FVC: forced vital capacity; SpO<sub>2</sub>: oxygen saturation; SD: standard deviation; FEV<sub>1</sub>: forced expiratory volume in 1 second

**Table 4 -** Chronic and intermittent colonization before and during the one-year treatment with dormase alfa in CF patients

	Age groups										
	6 -11 years			12-13 years			≥14 years				
	T0	T2	T4	T0	T2	T4	T0	T2	T4	T4	
n=77	n=67	n=60	n=13	n=11	n=10	n=59	n=49	n=38			
<i>Pseudomonas aeruginosa</i>											
Chronic	19/67 (28.4%)	22/58 (37.9%)	24/52 (46.2%)	3/12 (25.0%)	3/8 (37.5%)	1/7 (14.3%)	25/50 (50.0%)	18/38 (47.4%)	17/32 (53.1%)		
Intermittent	24/67 (35.8%)	21/58 (36.2%)	15/52 (28.8%)	5/12 (41.7%)	3/8 (37.5%)	4/7 (57.1%)	8/50 (16.0%)	4/38 (10.5%)	3/32 (9.4%)		
<i>Staphylococcus aureus</i>											
Chronic	14/66 (21.2%)	11/55 (20.0%)	13/51 (25.5%)	0/11	4/9 (44.4%)	2/9 (22.2%)	13/47 (27.7%)	9/40 (22.5%)	5/31 (16.1%)		
Intermittent	29/66 (43.9%)	24/55 (43.6%)	22/51 (43.1%)	8/11 (72.7%)	2/9 (22.2%)	4/9 (44.4%)	16/47 (34.0%)	9/40 (22.5%)	8/31 (25.8%)		
<i>Burkholderia cepacia</i>											
Chronic	0/46	0/46	1/41 (2.4%)	1/8 (12.5%)	1/8 (12.5%)	1/9 (11.1%)	1/39 (2.6%)	1/30 (3.3%)	1/24 (4.2%)		
Intermittent	1/46 (2.2%)	2/46 (4.3%)	1/41 (2.4%)	0/8	0/8	0/9	0/39	0/30	0/24		
<i>Stenotrophomonas maltophilia</i>											
Chronic	0/32	0/21	0/19	0/8	0/7	0/8	0/39	1/30 (3.3)	0/24		
Intermittent	1/32 (2.2%)	4/21(8.7%)	3/19 (7.3%)	0/8	0/7	0/8	1/39 (2.6)	0/30	1/24(4.2)		

T0: baseline visit; T2: 6-months follow-up visit; T4:12-months follow-up visit.

Data are shown as numbers and percentages. The number of patients varied across the follow up visits; n: number of patients

**Table 5 -** Use of routine concomitant treatments during the study follow-up

	Age groups										
	6-11 years			12-13 years			≥14 years				
	T0	T2	T4	T0	T2	T4	T0	T2	T4	T4	
n=77	n=67	n=60	n=13	n=11	n=10	n=59	n=49	n=38			
Respiratory physical therapy	56/76 (73.7%)	65/67 (97.0%)	55/60 (91.7%)	10/13 (76.9%)	9/11 (81.8%)	10/10 (100%)	34/57 (59.6%)	37/47 (78.7%)	27/37 (73.0%)		
Regular exercises	40/76 (52.6%)	40/67 (59.7%)	41/60 (68.3%)	7/13 (53.8%)	8/11 (72.7%)	6/10 (60.0%)	22/57 (38.6%)	25/48 (52.1%)	22/37 (59.5%)		
Bronchodilators	36/77 (46.8%)	26/67 (38.8%)	24/60 (40.0%)	9/13 (69.2%)	6/11 (54.5%)	6/9 (66.7%)	37/59 (62.7%)	23/47 (48.9%)	21/37 (56.8%)		
Antibiotics	44/76 (57.9%)	36/67 (53.7%)	32/60 (53.3%)	7/12 (58.3%)	4/11 (36.4%)	6/10 (60.0%)	28/56 (50.0%)	27/46 (58.7%)	16/36 (44.4%)		
Corticosteroids	17/77 (22.1%)	13/67 (19.4%)	11/60 (18.3%)	6/13 (46.2%)	4/11 (36.4%)	4/10 (40.0%)	18/59 (30.5%)	13/47 (27.7%)	14/36 (38.9%)		
Mucolytic agents	4/77 (5.2%)	1/67 (1.5%)	3/60 (5.0%)	-	-	-	2/59 (3.4%)	3/46 (6.5%)	1/37 (2.7%)		
Home oxygen*	2/77 (2.6%)	1/67 (1.5%)	1/60 (1.7%)	-	-	-	10/59 (16.9%)	6/48 (12.5%)	2/37 (5.4%)		
Assisted ventilation	-	-	1/60 (1.7%)	-	-	-	-	-	1/36 (2.8%)		
Pancreatic enzymes	63/77 (81.8%)	57/67 (85.1%)	54/60 (90.0%)	5/13 (38.5%)	6/11 (54.5%)	6/10 (60.0%)	28/58 (48.3%)	24/48 (50.0%)	18/37 (48.6%)		
Oral supplements	42/76 (55.3%)	36/65 (55.4%)	38/60 (63.3%)	5/13 (38.5%)	4/11 (36.4%)	6/10 (60.0%)	20/58 (34.5%)	17/47 (36.2%)	14/36 (38.9%)		
Vitamins	60/77 (77.9%)	50/67 (74.6%)	44/60 (73.3%)	8/13 (61.5%)	6/11 (54.5%)	6/10 (60.0%)	39/59 (66.1%)	30/49 (61.2%)	26/38 (68.4%)		
Non-hormonal anti-inflammatory drugs	1/74 (1.4%)	1/67 (1.5%)	1/59 (1.7%)	1/13 (7.7%)	2/11 (18.2%)	2/10 (20.0%)	-	2/48 (4.2%)	-		
Azithromycin	10/75 (13.3%)	9/67 (13.4%)	9/60 (15.0%)	3/13 (23.1%)	4/11 (36.4%)	3/10 (30.0%)	12/58 (20.7%)	15/48 (31.3%)	11/36 (30.6%)		
Diuretics	2/75 (2.7%)	2/67(3.0%)	1/60 (1.7%)	-	-	-	1/59 (1.7%)	0/48	-		
Insulin	1/75 (1.3%)	1/67 (1.5%)	1/60 (1.7%)	-	-	-	-	1/48 (2.1%)	2/37 (5.4%)		
Oral hypoglycemicant	-	1/60 (1.7%)	-	-	-	-	-	-	-		

\*Use at crisis, daily or only at night

lung disease, is a strong recommendation, grade A, with good level of evidence and substantial benefit<sup>(5)</sup>. It was also recommended for CF patients with mild lung disease by the European Consensus<sup>(17)</sup>. Our aim was to investigate whether the improvements observed in patients' QoL<sup>(14)</sup> would also reflect benefits in clinical *status*.

In the previous studies<sup>(14,15)</sup>, CF patients were divided into three age groups according to the original protocol of the CFQ-R<sup>(16)</sup>. The formal inclusion of CFQ-R questionnaires as a clinical outcome was essential, as it detected the impact of dornase alfa treatment over QoL, from the perspective of patients and their families. It allowed the identification of baseline reference values for QoL in the different age groups, and the progression of the QoL domains scores over the time<sup>(14,15,18)</sup>. The present paper was an attempt to rescue the outcomes of distinct age groups. Thus, it would be possible to make comparisons between these groups, to evaluate individual patients in relation to the baseline characteristics of their respective age groups, and to plan future strategies.

Patients aged 6 to 11 years were those who most benefited from the use of dornase alfa. A significant reduction in the number of emergency room visits due to acute exacerbations was coincident with improvement in the QoL Respiratory Domain of previous paper<sup>(14)</sup>. The significant improvement in the Shwachman-Kulczycki score observed in the older group can also be pointed as a positive outcome of the therapy, and when considered together with the favorable results in CFQ-R other domains<sup>(14)</sup>, it allows the conclusion that dornase alfa is an additional therapeutic option for CF. Recently, dornase alfa was included in the recommendations of the Ministerial Order SAS/MS, n° 224, emended in 2010<sup>(19)</sup>. Evidently the cost-benefit relationship of this therapeutics was carefully revised by ANVISA (National Agency of Sanitary Surveillance) before its implementation in routine usage<sup>(19)</sup>.

Regarding patients' characteristics, mean age at diagnosis was 9.3 years, ranging from <1 to 56 years, and the main clinical manifestations were pulmonary infections, malnutrition and pancreatic insufficiency, as in other studies. The CF diagnosis occurred late in all age groups (median age at diagnosis, 4.0 and 15.0 years); as already known, the late diagnosis results in worse prognosis of CF lung disease. Fortunately, improvements in age at diagnosis has been observed in recent Brazilian research<sup>(20)</sup>.

In our study,  $\Delta F508$  was the most frequent mutation detected in agreement with genotype distribution study of

Brazilian patients from five different states (overall frequency of 48%)<sup>(20,21)</sup>. According to the Cystic Fibrosis Foundation's Patient Report 2009, almost 91% of the CF patients have their mutations identified, and the  $\Delta F508$  mutation is present in near 90% of cases<sup>(1)</sup>. Mutations found in our study are among the most common mutations detected in CF<sup>(1,20)</sup>.

Persistent airway colonization has a devastating impact on patient's life span and contributes to local inflammatory response and to progressive deterioration of lung function with age<sup>(2)</sup>. *P. aeruginosa* and *S. aureus* are of primary importance in chronic infections. Gangell *et al.* suggested that pulmonary inflammatory response may vary according to the infecting organism, and *P. aeruginosa* was associated with greater levels of inflammation<sup>(22)</sup>. *S. aureus*, *P. aeruginosa* and *B. cepacia* complex are the most important bacteria in CF lung infections; however, other agents are emerging as *S. maltophilia*, *A. xylosoxidans*, methicillin-resistant *Staphylococcus aureus* (MRSA) and nontuberculosis mycobacteria<sup>(20,23,24)</sup>. In our study population, a similar pattern of microbiology distribution was observed, with prevalence of infections by *P. aeruginosa* and *S. aureus*, and the emergence of isolate cases of oxacilin-resistant *S. aureus*, *Aspergillus spp*, *K. pneumonia*, and other gram-negative bacteria, predominantly in the older age group of patients. Findings for the age group 6 to 11 are especially worrying as 64% of patients were already intermittently or chronically colonized by *P. aeruginosa* at the initiation of the therapy (T0), and this rate increased to 75% until the end of the follow-up period. In agreement with Bonestroo *et al.*<sup>(25)</sup>, we have not observed a positive effect of dornase alfa in reducing pulmonary colonization. However, our finding contrasts with results of a randomized study by Frederiksen *et al.*<sup>(26)</sup>, who demonstrated a significant reduction of airway colonization by gram-negative or gram-positive bacteria with dornase alfa, with the exception of *P. aeruginosa*. In this respect, we may speculate that our colonization results are not consistent with the clinical outcomes observed: during dornase alfa treatment there was a significant reduction in the number of hospitalizations, and emergency visits due to acute exacerbations in the younger group, in agreement to other studies<sup>(27)</sup>.

Treatment strategies for CF are known to be demanding and have a complex scheme. Analysis of procedures performed in the daily routine, several times per day, including respiratory physical therapy, regular exercises, bronchodilators, oral and inhaled antibiotics, corticosteroids, dornase alfa, pancreatic enzymes and vitamins supplements,

besides home oxygen and insulin in selected cases, showed that patients and their families are constantly occupied in performing time-consuming routines and complex treatment schedules imposed by the disease, and therefore, have limited time for leisure and a poor quality of life<sup>(28)</sup>.

A systematic review addressed the impact of dornase alfa compared to placebo or other mucolytics on morbidity and mortality, and found that the use of dornase alfa for a period over one month until two years was associated with an improvement in lung function<sup>(29)</sup>. In our study, treatment with dornase alfa did not promote significant changes in a mean FEV<sub>1</sub> after one year of use, as compared to baseline, in all age groups. It is known that an important aspect of CF evolution and prognosis is the rate of lung function decline, and slowing this rate is crucial for long-term survival<sup>(13)</sup>. Recently, an association between the use of dornase alfa for a period of two years and the reduction in the rate of FEV<sub>1</sub> decline was observed in a large prospective observational study<sup>(13)</sup>. In a placebo controlled trial investigating the effects of long-term treatment with dornase alfa, it was shown that in young patients with CF, dornase alfa maintains lung function and reduces respiratory tract exacerbations. Considering that the progressive decline in lung function is a hallmark of CF, maintenance of lung function should be highlighted as an important achievement of the treatment<sup>(27)</sup>. Similarly, our findings show a stabilization of lung function parameters at 6 and 12 months of dornase alfa, with no reductions in FEV<sub>1</sub> over the one year period as it would be expected<sup>(30)</sup>. Although not statistically significant, the absolute increase of 3% in the final mean of VEF<sub>1</sub> in the younger group may be considered as a progress from a clinical perspective. This improvement or maintenance of VEF<sub>1</sub> values confirms other findings showing the advantages of early introduction of dornase alfa for patients with mild disease (VEF<sub>1</sub> >80%) in the reduction of lung function decline rate<sup>(27)</sup>. Delaying the decline in organ functions is one of the main goals of current treatments for CF, and initiation of dornase alfa early in the life is one of the identified factors associated with slower rate of decline in lung function<sup>(31)</sup>.

The importance of this publication resides on the fact that it was mostly prospective, following a standardized documentation used in all 16 CF centers, with a significant number of patients. Although information collected at T0

was based on retrospective data, it was important to obtain the standard patterns of care and clinical characteristics of this population before treatment. Obtaining baseline data of a population to allow future comparisons is one of the elements that contribute to the good quality of research<sup>(18,32)</sup>. However, an extended duration of the study, a wide spread of CF Centers across Brazil and CF patient personal problems had contributed to less than ideal register of collecting data, with missing data in all age groups, that was considered a limitation of the study.

The lack of a control group not treated with dornase alfa and the heterogeneity of some clinical procedures adopted in the participating centers are also limitations of this study. The lack of a comparison group, not treated with dornase alfa, is a limitation that impairs a complete investigation about the benefits of the drug in CF patients. In view of the current recommendations regarding the use of dornase alfa, it was decided not to have a control group, as the use of placebo or another mucolytic drug would be ethically questionable<sup>(5,33)</sup>. Nevertheless, in our study, subjects served as their own controls as clinical information of the last 6 months prior to the study entry were rescued for each patient. Regarding variations in clinical management of the various centers, regular updating and contact between researchers have minimized differences in basic care approaches and monitoring of patients. Further multicenter research will be welcomed to clarify many clinical aspects and outcomes of CF patients without the limitations imposed by this study.

In summary, we have observed that CF patients have significant disease morbidity despite all routine therapies that they receive in CF centers. Dornase alfa promotes stabilization of lung function parameters, including FEV<sub>1</sub>, in patients aged 6–11 and <sup>3</sup>14 years, and exerts a favorable impact on the clinical profile of CF patients irrespective of the age.

## **Acknowledgments**

This study received technical support and medical advises from Dr. José Roberto Jardim PhD, and an educational grant from Roche, Brazil.

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