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Clinical and functional course of patients with cystic fibrosis treated with lumacaftor/ivacaftor at a children's hospital. A case series

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ABSTRACT

Cystic fibrosis transmembrane regulator (CFTR) modulators treat defective CFTR protein. Our objective is to describe the course of children with cystic fibrosis treated with lumacaftor/ivacaftor.

This is a case series of 13 patients aged 6 to 18 years with ≥ 6 months of treatment. Forced expiratory volume in the first second (FEV1), body mass index (BMI) Z-score, antibiotic therapy/year, before treatment and for 24 months after treatment were analyzed.

At 12 months (9/13) and 24 months (5/13), the median change in the percent predicted FEV1 (ppFEV1) was 0.5 pp (-2–12) and 15 pp (8.7–15.2) and the BMI Z-score was 0.32 points (-0.2–0.5) and 1.23 points (0.3–1.6). In the first year, in 11/13 patients, the median number of days of antibiotic use decreased from 57 to 28 (oral) and from 27 to 0 (intravenous). Two children had associated adverse events.

Keywords: *cystic fibrosis; lumacaftor; ivacaftor; respiratory tract infections; pediatrics.*

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INTRODUCTION

Cystic fibrosis (CF) is an inherited, autosomal, recessive disease characterized by exocrine gland dysfunction. The causative gene encodes a cystic fibrosis transmembrane regulator (CFTR), a chloride-bicarbonate channel protein.[1] The most frequent mutation is ΔF508.[2–4] The abnormal function or absence of CFTR causes a defect in the ionic composition and hydration of secretions from different organs. It is typically accompanied by chronic and progressive pulmonary disease[1,5] and exocrine pancreatic insufficiency leading to malabsorption and growth failure.[3,6] Respiratory involvement is the leading cause of morbidity and mortality.[1,3]

CFTR modulator therapies target the underlying defect in the protein to restore its function. Lumacaftor, a corrector, improves intracellular trafficking of the protein to the membrane, and ivacaftor, an enhancer, improves channel opening once inserted.[2,7] The lumacaftor/ivacaftor combination is indicated in patients with homozygous ΔF508 mutation. It was approved by the United States Food and Drug Administration (FDA) in 2015, initially for patients older than 12 years[8] and, in 2018, for patients older than 2 years.[9]

In Argentina, ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and tezacaftor/elexacaftor/ivacaftor are available for patients as of 6 years of age.[10]

The objective of this study is to describe the course of clinical and pulmonary function of children with CF treated with lumacaftor/ivacaftor manufactured in Argentina.

METHODS

Clinical case series. The medical records (MRs) of patients who met the inclusion criteria were reviewed: 6 to 18 years of age, with CF, homozygous ΔF508 mutation, treated with lumacaftor/ivacaftor (manufactured in Argentina) for ≥ 6 months, seen at the CF center of Hospital Garrahan in the City of Buenos Aires, Argentina, between December 2018 and December 2021. Patients whose MR data were incomplete were excluded.

The protocol was approved by the Ethics Committee, and the informed consent was waived.

The variables of interest were analyzed at 12 months before treatment initiation, at baseline, at 6 months and, where available, at 12, 18, and 24 months after treatment.

Lung function was assessed by spirometry. The baseline value of forced expiratory volume in the first second (FEV1), estimated as the average of ≥ 2 measurements for each time period analyzed and expressed as a percent predicted of FEV1 (ppFEV1), was measured. The spirometric values proposed by the Global Lung Function Initiative 2012 were used.

Nutritional status was assessed using the body mass index (BMI) and the BMI Z-score.

Cumulative antibiotic use was analyzed by calculating the total number of days of antibiotic use for each patient/year as a surrogate measure of respiratory exacerbation.

Sweat test values were compared before treatment and 1–3 months after treatment. Samples were collected with a Macroduct® device. The quantitative value of sodium chloride (NaCl) was recorded.

Treatment-related adverse events were observed using complementary tests: ECG alterations, increased transaminase levels, or altered fundus oculi.[11,12]

The R Studio software was used for the descriptive analysis. Qualitative variables were expressed as percentages or proportions, and quantitative variables, as median and interquartile ranges [IQR].

RESULTS

A total of 19 MRs of patients treated with lumacaftor/ivacaftor were reviewed. Of these, 6 were excluded: 5 due to incomplete MR and 1 due to medication discontinuation secondary to oral route intolerance. The clinical and demographic characteristics of the 13 patients are summarized in *Table 1*. A total of 5/13 children completed 24 months of follow-up.

Data were obtained for all patients (13/13) before treatment initiation and at 6 months, for 9/13 patients at 12 months, for 7/13 at 18 months, and for 5/13 at 24 months for the lung function and nutritional status variables.

The median annual baseline ppFEV1 before treatment initiation was 61.2% (48–72.3), with a median increase from baseline of 1.8 percentage points (pp) (-3.5–7.7), 0.5 pp (-2–12), 6.7 pp (2.5–14.6), and 15 pp (8.7–15.2) observed at 6, 12, 18, and 24 months after treatment, respectively (*Figure 1*). No improvement in lung function was observed in children with an annual baseline ppFEV1 before treatment initiation ≤ 40% (2/13) or > 80% (3/13), with a median change in ppFEV1 at 12 months of -7.5 pp and 0.5 pp, respectively.

Table 1. Characteristics of the population

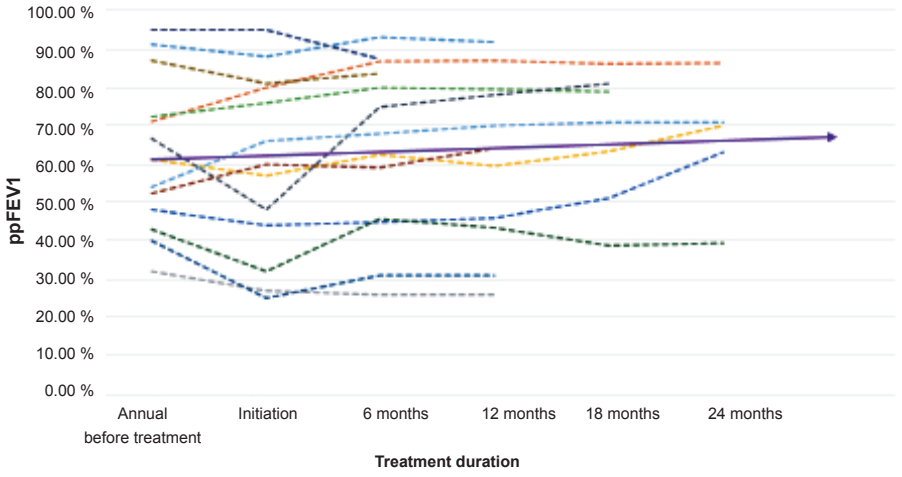
Characteristics of the population	n = 13
Male sex - n/total	7/13
Age (years) at treatment initiation *	13 (9–15)
Annual baseline ppFEV1 at treatment initiation *	61.2% (48–72.3)
BMI (kg/m^2) at treatment initiation *	16.4 (14.7–17.7)
Chronic infection ** - n/total	
MRSA	4/13
PA	4/13
Comorbidities - n/total	
Liver transplantation	1/13
Chronic respiratory insufficiency	1/13

**Variable with non-normal distribution, described as median and interquartile range.*
***Chronic infection: presence of the same microorganisms in > 50% of cultures (min. 4 specimens) in the past 12 months*[7]
ppFEV1: percent predicted of forced expiratory volume in the first second.
BMI: body mass index.
MRSA: methicillin-resistant Staphylococcus aureus.
PA: Pseudomonas aeruginosa.

The median BMI before treatment initiation was 16.4 kg/m^2 (14.7–17.7). A median BMI Z-score change from baseline of -0.11 points (-0.2–0.5), 0.32 points (-0.2–0.5), 0.68 points (0.1–1), and 1.23 points (0.3–1.6) was observed at 6, 12, 18, and 24 months after treatment, respectively (*Figure 2*).

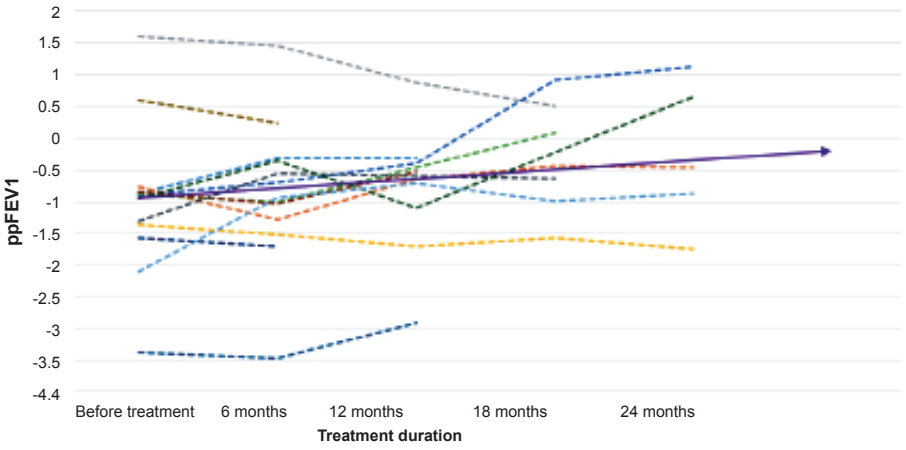
In relation to antibiotic use/year, data were obtained from 11/13 patients at 12 months after treatment and from 5/13 at 24 months after treatment. The median oral antibiotic use/year was 56 days (18–63) in the year before treatment, 28 days (0–46) in the first year, and 14 days (7–21.5) in the second year after treatment. The median IV antibiotic use/year was 27 days (12.5–35.5) the year before treatment and 0 days (0–32.5, 0–15) the first and second year after treatment initiation. Patients with a baseline ppFEV1 ≤ 40% (2/13) who showed no improvement in lung function required oral antibiotics for 63 and 42 days/year before treatment; 0 and 21 days/year during the first year after treatment. In relation to IV antibiotics, the time of use decreased in 1 patient and remained the same in another: they

Figure 1. Course of ppFEV1



The baseline ppFEV1 values for each patient according to the time period of treatment with lumacaftor/ivacaftor are shown as dotted lines, whereas the trend of median values is shown as a solid line.
ppFEV1: percent predicted of forced expiratory volume in the first second.

Figure 2. Course of BMI Z-score



The BMI Z-scores for each patient according to the time period of treatment with lumacaftor/ivacaftor are shown as dotted lines, whereas the trend of median values is shown as a solid line.
BMI: body mass index.

received antibiotics for 70 and 42 days/year before treatment; 0 and 42 days/year in the first year after treatment, respectively.

Six patients had sweat tests before and after treatment, with a median NaCl of 120 mEq/L (107–125) before treatment and 110 mEq/L (103.5–112.5) after treatment, which accounted for an 8.3% reduction.

One child had an increase in transaminase levels < 3 times the normal value at 1 month and another had mild lens opacity at 2 months after treatment. None of them required discontinuation of medication.

A patient with liver transplantation received lumacaftor/ivacaftor with good tolerance and no increase in transaminase levels.

DISCUSSION

In this case series, patients showed an increase in ppFEV1 greater than what had been reported in the bibliography. The pivotal, phase 3 studies, TRAFFIC and TRANSPORT, assessed the efficacy of the lumacaftor/ivacaftor combination versus placebo in patients ≥ 12 years and found a mean absolute change in ppFEV1 from 2.6 to 4.0 pp ($p < 0.001$) at 6 months of treatment.[8] The PROGRESS study, which assessed the long-term efficacy of lumacaftor/ivacaftor in patients ≥ 12 years, showed an improvement in ppFEV1 at 24 months of treatment (least squares mean change 1.1 pp; 95% CI 0–2.2, $p = 0.05$).[13]

Chilvers et al. also observed an improvement in ppFEV1 in children aged 6-11 years at 30 months of treatment with lumacaftor / ivacaftor (least squares mean change 3.1 percentage points; 95% CI 1.0 to 5.1).[14]

Study patients showed a median BMI Z-score change of 1.23 points at 24 months after treatment. Both TRANSPORT and PROGRESS studies reported increases in the absolute value of BMI.[8] The PROGRESS study found an increase in BMI at 30 months of treatment (least squares mean change 0.96 pp; 95% CI 0.81–1.11, p < 0.0001).[13]

Consistent with our findings, the combined analysis of the TRAFFIC-TRANSPORT studies showed a decrease in pulmonary exacerbations between 30% and 39% in the lumacaftor/ivacaftor group versus the placebo group.[8] In the *post hoc* analysis, these studies showed that the reduction in respiratory exacerbations occurred even in patients who did not show early improvements in lung function.[15] Likewise, the PROGRESS study found an exacerbation rate of 0.65 events/patient/year (95% CI: 0.56–0.75) in the treatment group versus 1.14 in the control group (95% CI: 0.97–1.34).[13]

Although described adverse events include increased transaminase levels and lens opacity, which may require monitoring, the lumacaftor/ivacaftor combination has proven to be safe in pediatrics.[8,12–14]

This is the first study to describe the effect on the short- and medium-term course of children with CF receiving lumacaftor/ivacaftor in Argentina seen at a referral center. Given the small sample size and lack of a control group, no statistical tests were done with the results, and data should be interpreted with caution.

Although this medication combination is losing validity due to the recent availability of tezacaftor/elexacaftor/ivacaftor, which is more effective and safer in a broader range of patients, lumacaftor/ivacaftor is a valid option as a bridge until access to tezacaftor/elexacaftor/ivacaftor is achieved.

CONCLUSIONS

In this case series, children with CF treated with lumacaftor/ivacaftor showed an improvement in the ppFEV1 and BMI Z-score and a reduced use of antibiotics for respiratory exacerbations. ■

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