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Title: ADHERENCE TO LUMACAFITOR-IVACAFITOR THERAPY IN PATIENTS
WITH CYSTIC FIBROSIS IN FRANCE

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Introduction

Cystic Fibrosis (CF) is the most common genetic disease in Caucasian populations. It affects over 43,000 people in Europe, and almost 7,000 in France [1]. In CF, the mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene induce the production of an altered CFTR protein unable to ensure regulation of epithelial ion transport. This contributes to a thick and sticky mucus production obstructing airways and glands and leading to multi-organ complications. The disease is characterized by a great clinical and genetic heterogeneity. Over 2000 mutations have been reported in the CFTR gene [2]. With a 70% frequency, deletion of the codon for phenylalanine at position 508 is the most common disease-causing mutation [3]. In the last few years, efforts in implementation of standards of care have been made, including newborn screening and early specialized care in multidisciplinary CF care centers. With improvements in managing CF, life expectancy is increasing progressively and CF is changing from a childhood disease to an adult one [4]. This progress involves complex and time-consuming cares with daily treatments regimens, chest physiotherapy, nutritional support and physical activity [5]. Due to the increasing burden of treatment, therapeutic adherence has become a priority issue in managing CF [6]. According to a recent literature review, medication adherence among patients with CF is suboptimal [5]. Rates of adherence varied greatly depending on measurement methodologies, drug classes and patients' characteristics [6]. Low adherence to CF therapies has been associated with poor health outcomes such as the risk of hospitalization, a longer hospital stay, pulmonary exacerbations and the decline in the baseline lung function, which remains the primary reason for premature death in CF [7, 8]. So far, drugs available for CF patients only treat the disease symptoms' in order to slow its progression. Research efforts focused on developing new therapeutic approaches. In 2012, licensing of ivacaftor (Kalydeco®), a CFTR modulator therapy, marked a new era in the treatment of CF. For the first time, a drug that targeted the underlying defect of the disease, which was caused by specific mutations, was available. Ivacaftor has been approved for patients from 6 years and older with a gating mutation in the CFTR gene, including G551D and R117H, which represent a little less than 3% of the European CF population [9]. In 2015, lumacaftor-ivacaftor (LUM-IVA) combination (Orkambi®) received European Union (EU) approval for patients aged 12 and older with two copies of the F508del mutation in the CFTR gene. In January 2018, the EU extended the marketing approval of Orkambi® to include children aged 6 to 11, making it available for a largest patients' population. In Europe, around 40% of the CF population would benefit from

Orkambi® [9]. CFTR modulator therapies were shown to be effective in improving lung function and reducing the number of exacerbations requiring hospital admission or antibiotic therapy [10]. The introduction of CFTR modulator therapies offers great hope for patients but also increases treatment burden and costs. This raises the question of adherence for these innovative medicines which is essential to achieve expected clinical benefits. There are only a few studies that have reported adherence to CFTR modulator therapies. Adherence to ivacaftor therapy has been assessed in three small cohort studies [11–13]. As far as we know, no study has investigated the adherence to ivacaftor-lumacaftor combination. Given the emergence of CFTR modulator therapies, there is a need to measure and evaluate adherence to these new medicines in order to understand patients' behavior and optimize CF management. This retrospective study has two objectives: 1) to evaluate 1-year adherence in patients newly initiating lumacaftor-ivacaftor therapy; 2) to investigate factors that are potentially associated with lumacaftor-ivacaftor's adherence.

1. Methods

1.1. Data source and sample selection

Patients were recruited from five French CF centers in Auvergne Rhône-Alpes region: two pediatric centers, two adult ones, and one mixed center. Patients included met the following criteria : (1) confirmed diagnosis of CF with homozygous F508del-CFTR mutation (the only approved genotype at the time of the study), (2) age ≥ 12 (age was calculated at the initiation date), (3) initiation of lumacaftor-ivacaftor therapy after March 14, 2016 (date of marketing authorization in France) and before November 1st, 2017 (allowing at least 12 months of follow up at the time of data collection), [4] prescription of at least 6 consecutive months of treatment after initiation. Patients were excluded if they were transferred to another CF center during the observation period and if their treatment was interrupted more than 45 days during the observation period of 6 months and 91 days during the observation period of 12 months. Data were collected retrospectively in November 2018. A medical chart review was conducted to extract clinical and demographic data including age, gender, body mass index (BMI), CF center of enrollment, place of residence, comorbidities (pancreatic insufficiency, diabetes, chronic *Pseudomonas aeruginosa* infection), percent predicted forced expiratory volume in 1s (ppFEV1), health status (death, transplantation and number of days of hospitalization). At the time of the study, in France, lumacaftor-ivacaftor therapy was only available in hospital pharmacies. To obtain patients pharmacy refills, hospital pharmacies providing lumacaftor-ivacaftor therapy to patients

were contacted. Adherence to lumacaftor-ivacaftor was calculated using proportion of days covered (PDC), which is the total number of medication-covered days divided by the number of days in a certain period. PDC was calculated for 6 and 12 months after the date of treatment initiation, excluding days of hospitalization. Adherence to lumacaftor-ivacaftor therapy was defined as a PDC \geq 80% [14]. Factors potentially associated with adherence that were assessed were age, gender, and travel time from the place of residence to the hospital pharmacy and pulmonary function before treatment initiation. Travel time from the place of residence to the hospital pharmacy was calculated using the ZIP code and Google® maps. It was estimated in fluid traffic conditions and the shortest route was chosen. Pulmonary function before treatment's initiation was evaluated using the best measurement of ppFEV1 in the previous 6 months. Individual subject observation periods began from the date of treatment initiation for 12 consecutive months. Demographical, clinical, and laboratory data were extracted from patients' records, with permission from the Institutional Review Board of our hospital on October 24, 2018.

1.2. Statistical analyses

Continuous variables were described as means and standard deviations (SD). Categorical variables were described as frequencies. Patients were categorized into 2 groups, adherent (PDC \geq 80%) and non-adherent (PDC < 80%) at 6 and 12 months and their clinical characteristics were compared using χ^2 test or the exact Fisher test. Multivariate logistic regression analyze was conducted to examine the association between lumacaftor-ivacaftor adherence and different factors: travel time from the place of residence to pharmacy, ppFEV1, gender and age. A p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 21.0.

3. Result

3.1. Patients' characteristics

Out of the 963 CF patients followed up in Auvergne Rhône-Alpes CF centers, 192 patients were treated with lumacaftor-ivacaftor. After applying the inclusion and exclusion criteria, 96 patients were included in the final cohort for analysis. All of them were homozygous for the F508del-CFTR mutation. Table 1 shows the demographic and clinical data of the 96 patients included. The mean age of the cohort was 22 years (\pm 9). The overall cohort had predominantly adults (55% vs 45% under 18), male (54%). Mean ppFEV1 was 77% (\pm 25), with well-preserved lung function in 57% (ppFEV1 > 70%). All patients had an altered exocrine pancreatic function; cystic fibrosis-related diabetes was diagnosed in

13%, and chronic *Pseudomonas aeruginosa* colonization in 37%. The mean number of hospitalization days per patient was 3.5 days (\pm 12.4). None of the patients died or was transplanted during the observation period. Fifty-one percent had a maximum travel time of 20 minutes from their residence to pharmacy).

3.2. Adherence rates

The mean PDC was $96\% \pm 14$ (ranged from 46% to 150%, >100% was due to an over-refilling by 12 patients) at 6 months, and $91\% \pm 17$ (ranged from 34% to 138%, >100% was due to an over-refilling by 7 patients) at 12 months. The proportion of adherent patients, defined as $PDC \geq 0.80$, was 89% ($n=86$) and 83% ($n=80$) at 6 and 12 months respectively. Demographic and medical characteristics compared between adherent and non-adherent patients at 12 months are highlighted in Table 1. Based on $PDC \geq 80\%$ for adherence, patients in the age range of 18 to 25 years were significantly less adherent as compared to patients from 12 to 17 years old, 26 to 35 and over 35 years of age ($p = 0.006$). There was no statistically significant difference in other characteristics when comparing adherent and non-adherent patients. In the logistic regression model predicting $PDC \geq 0.80$, after an adjustment for potential confounding criteria, there was a non-significant relationship between adherence and ppFEV1 and age. Patients with higher ppFEV1 may be more adherent to treatment and patient between 12 and 17 years old may also be more adherent compared to patients between 18 and 25 years old (Table 2).

4. Discussion

This retrospective study evaluated adherence in patient with newly initiating lumacaftor/ivacaftor therapy. By using pharmacy refill data, high levels of adherence at 6 months and 12 months after treatment initiation were found. Up to our knowledge, this is the first study that reports adherence to lumacaftor-ivacaftor therapy in real-life. These findings suggest that adherence to lumacaftor-ivacaftor, the first CFTR modulator therapy approved for patients homozygous for the F508del-CFTR mutation, is higher than adherence to other treatment routines in CF. Multiple studies have documented moderate to low adherence to inhaled CF treatments [15–17], airway clearance therapy [18] and oral CF treatments such as pancreatic enzyme replacement therapy [19–21], vitamins [19, 21] and oral azithromycin [22, 23]. High adherence to CFTR modulators and low adherence to other CF treatments is consistent with findings from the few studies that have reported high adherence to ivacaftor among patients with G551D mutation [11–13]. Results of this study suggest that patients from 18 to 25 years

of age may be less adherent to lumacaftor-ivacaftor therapy. Emerging adulthood (ages 18-25) is a period marked by many changes (starting career, transitions healthcare teams, changing in residence, development of new relationships, autonomy for the management of treatment) that may influence the adherence to treatment [24]. Other studies have demonstrated a decline of adherence among this age group [18, 25]. In this study, after adjusting for potential confounders, there was a non-significant relationship between adherence and ppFEV1 and age and variation in adherence. The lack of statistical significance may be due to the small sample size for non-adherent patients. The high level of adherence to lumacaftor-ivacaftor therapy measured in this study may be explained by several factors. First, considering the high cost of Orkambi®, it is important to note that in France, Orkambi® is covered by public health insurance. In countries where Orkambi is not covered by health insurance, its cost might be a barrier to adherence. In France at the time of this study, Orkambi® was only available in hospital's pharmacies (with no drug shortage), which might contribute to over estimation of adherence in this study, as it was shown that difficulties with access to medication supply has been correlated to poor medication adherence [26]. In addition, our patients were closely monitored during the first year after the treatment initiation which may have encouraged healthcare provider-patient communication and relationship and by that had enhanced adherence [26]. Finally, patient associations and medias have spread optimistic messages about this innovative precision medicine which may have positively influenced patients' beliefs about this medication and so contributed to enhance their adherence [19, 27]. This study has a small sample size and a small number of patients classified as non-adherents which limits the analysis of potential factors related to non-adherence. Another limitation in this study is that the pharmacy refill data was collected by contacting each patient's pharmacy and not by using insurance data as it is usually used in studies measuring adherence with PDC [28]. It cannot ensure the correctness of the transmitted data and it is possible that patients sometimes picked up their medication in another pharmacy than the usual pharmacy mentioned in their medical records. However, to avoid overestimated non-adherence, for each patient with a medication gap, the pharmacist was contacted again to ensure that the transmitted data was correct. The patient was also contacted and asked about all pharmacies in which he picked up his treatment. As Orkambi® is a long-term therapy, it would be interesting to evaluate adherence for a longer period than 12 months. Indeed, among patients with chronic illness, adherence to treatment usually decreases over time. Finally, although the estimation of adherence by a retrospective analysis

of pharmacy records reflects the global adherence, it cannot be assumed that the medications obtained in pharmacy are actually taken by patients. Despite all these limitations, this study provides interesting information about real life lumacaftor-ivacaftor adherence behavior among patients with CF. High level of adherence for this new medication is encouraging. Other CFTR modulators are in the pipeline and in a few years more patients might benefit from such therapies. Optimal adherence would be required to achieve full health outcomes benefits. Considering the economic cost of these new treatments, adherence represents a medical and economic challenge. This was the first study to evaluate lumacaftor-ivacaftor adherence during the first year of treatment among French patients with CF in real life. The study reported a high level of adherence to this innovative therapy.

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Conflicts of interest

The authors declare that they have no conflicts of interests.

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Figure 1. Consort diagram of patient enrollment

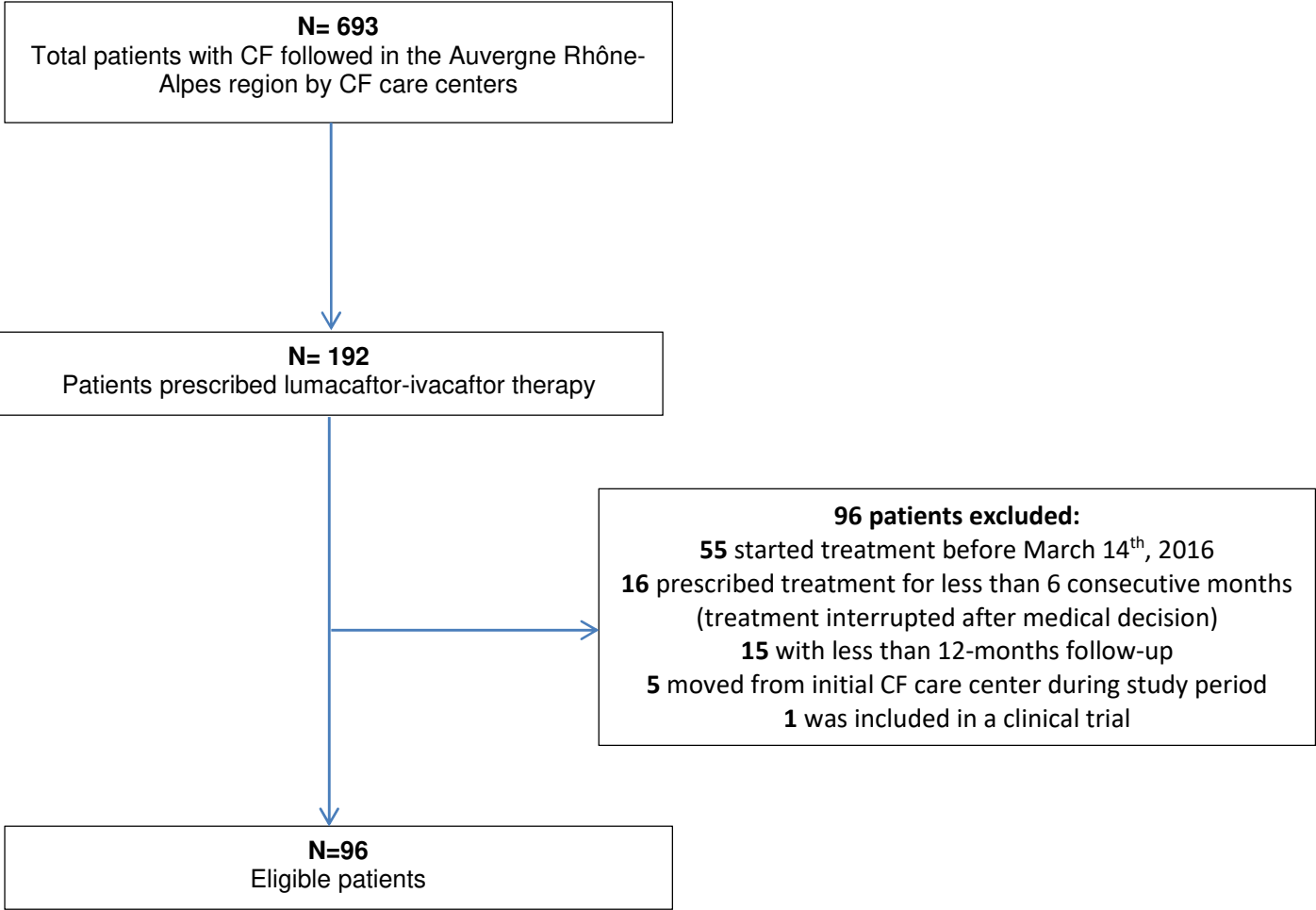


Table 1. Population characteristics according to adherence at 12 months

| | Entire study cohort (96 patients) | Patients adherent to LUM/IVA (80 patients) | Patients non- adherent to LUM/IVA (16 patients) | P-value |
|---|--------------------------------------|--|--|---------|
| | n(%) | n(%) | n(%) | |
| Age (years) | | | | |
| 12-17 | 43 (44.8) | 38 (47.5) | 5 (31.3) | 0.01 |
| 18-25 | 22 (22.9) | 13 (16.3) | 9 (56.3) | |
| 26-35 | 20 (20.8) | 19 (23.8) | 1 (6.3) | |
| >35 | 11 (11.5) | 10 (12.5) | 1 (6.3) | |
| Percent predicted FEV₁ (%) | | | | |
| ≤30 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.36 |
| 31-50 | 17 (17.7) | 14 (17.5) | 3 (18.8) | |
| 51-70 | 24 (25.0) | 18 (22.5) | 6 (37.5) | |
| >70 | 55 (57.3) | 48 (60) | 7 (43.8) | |
| BMI (kg/m²) | | | | |
| ≤18.5 | 34 (35.4) | 27 (33.8) | 7 (43.8) | 0.2 |
| 18.6-25 | 60 (62.5) | 52 (65.0) | 8 (50.0) | |
| >25 | 2 (2.1) | 1 (1.3) | 1 (6.3) | |
| Travel time from residence to pharmacy (min) | | | | |
| ≤20 | 49 (51.0) | 42 (52.5) | 7 (43.8) | 0.12 |
| 21-40 | 34 (35.4) | 30 (37.5) | 4 (25) | |
| 41-60 | 12 (12.5) | 7 (8.8) | 5 (31.3) | |
| >60 | 1 (1.0) | 1 (1.3) | 0 (0.0) | |
| Gender | | | | |
| Males | 52 (54.2) | 45 (56.3) | 7 (43.8) | 0.36 |
| Females | 44 (45.8) | 35 (43.8) | 44 (56.3) | |
| Chronic <i>Pseudomonas aeruginosa</i> | | | | |
| Yes | 35 (36.5) | 27 (33.8) | 8 (50.0) | 0.218 |
| No | 61 (63.5) | 53 (66.3) | 8 (50.0) | |
| Pancreatic insufficiency | | | | |
| Yes | 96 (100) | 80 (100) | 16 (100) | / |
| No | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Cystic fibrosis related diabetes | | | | |
| Yes | 12 (12.5) | 11 (13.8) | 1 (6.3) | 0.68 |
| No | 84 (87.5) | 69 (86.3) | 15 (93.8) | |

Table 2. Factors associated to patient adherence at 12 months: results of the multivariate logistic regression

| | Adjusted Odds Ratio | 95% Confidence Interval | P-value |
|--|----------------------------|--------------------------------|----------------|
| Male vs. Female | 1.3 | 0.4 – 4.2 | 0.67 |
| Age (year)* | 1.13 | 1.004 – 1.28 | 0.04 |
| BMI** | 0.8 | 0.6 – 1.18 | 0.15 |
| ppFEV1*** | 1.04 | 1.005 – 1.08 | 0.02 |
| Chronic Pseudomonas aeruginosa infection | 0.5 | 0.14 – 1.74 | 0.27 |
| Travel time from residence to pharmacy (min)**** | 0.9 | 0.74 -1.08 | 0.24 |
| | | | |

*for each additional year of age

**for each additional unit of BMI

***for each additional percent of FEV1pp

****for each 5 additional minutes of travel time