

First experience in Switzerland in Phe508del homozygous cystic fibrosis patients with end-stage pulmonary disease enrolled in a lumacaftor-ivacaftor therapy trial – preliminary results

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Summary

AIMS OF THE STUDY: Cystic fibrosis is the most common genetic disorder in Caucasians. The combination of the cystic fibrosis transmembrane conductance regulator (CFTR) corrector lumacaftor / potentiator ivacaftor (LUM/IVA) has been shown to increase forced expiratory volume in 1 second (FEV₁) moderately, but predominantly reduce acute exacerbation rate (AER) in Phe508del homozygous cystic fibrosis patients; however, patients with FEV₁ <40% predicted were excluded from studies. We used LUM/IVA on a “compassionate use” basis in cystic fibrosis patients with end-stage pulmonary disease. Our aim was to evaluate if this patient cohort tolerates LUM/IVA treatment and if there is clinical stabilisation. Lung transplantation (LTX) is the ultimate treatment option for these patients despite maximal therapy. If LTX candidates stabilise clinically, conditions for LTX, when it is indicated, improve. This is particularly important in countries such as Switzerland with a low organ donation rate and long waiting times for suitable donor organs.

METHODS: We included all patients from the Adult Cystic Fibrosis Centre at the University Hospital Zurich with Phe508del homozygous genotype and a predicted FEV₁ <40% or being evaluated or already listed for LTX. Clinical outcome data comprised AER, 6-minute walking distance (6-MWD), FEV₁, forced vital capacity (FVC), mid-expiratory flow (MEF 25–75%), sweat chloride, body mass index (BMI) and quality of life. Respiratory-related adverse events (RAEs) were recorded. LUM/IVA treatment was initiated at a low dose and the dose increased stepwise.

RESULTS: Twenty patients were on trial with LUM/IVA; at the cut-off date, 6-month follow-up was complete for 10 patients. RAEs were severe and occurred early. The dropout rate due to RAE or lack of clinical success was 20%. Median AER decreased from 2.5 in the 6 months pre-treatment to 1 during the observation period. FEV₁ increased from 32 to 34.5% predicted, $p = 0.292$. The

6-MWD increased by a median 33 m ($p = 0.6086$). Sweat chloride decreased significantly by a median of 25 mmol/l ($p = 0.0003$). Median BMI increased from 19 to 19.9 kg/m² ($p = 0.1488$). At the cut-off, three previously listed patients were paused on the transplant waiting list.

CONCLUSION: Phe508del homozygous cystic fibrosis patients with end-stage pulmonary disease tolerated LUM/IVA, although RAEs occurred early and were severe. This positive finding was probably due to the stepwise dose increases. There was clinical benefit mainly from reduction in AER and stabilisation of lung function. We propose that all suitable Phe508del homozygous cystic fibrosis patients with end-stage pulmonary disease should have a trial of LUM/IVA treatment in experienced centres.

Key words: cystic fibrosis, CFTR-modulator, end-stage pulmonary disease

Introduction

Cystic fibrosis, the most common genetic disorder in Caucasians, is caused by autosomal recessive mutations of the cystic fibrosis transmembrane conductance regulator (CFTR), an anion channel expressed on the apical surfaces of epithelial cells in airways, pancreatic ducts and other tissues. In Europe, 1 in 2000–3000 newborns are affected by cystic fibrosis [1, 2]. CFTR mutations can be categorised into seven classes on the basis of the aberrant CFTR synthesis or function [3].

As there is currently no cure for cystic fibrosis, progressive lung disease is the leading cause of death. New treatments targeting the CFTR protein in patients with gating mutations are promising [4]. Recently, a combination of the CFTR corrector lumacaftor (LUM) and CFTR potentiator ivacaftor (IVA) has been shown to moderately increase the primary study endpoint of forced expiratory volume in 1 second (FEV₁), but predominantly to reduce the acute exacerbation rate in Phe508del homozygous patients with cystic fibrosis [5]; however, patients with a FEV₁ <40%

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predicted were excluded from this and other CFTR modulator trials [4, 5].

LUM/IVA was approved by the US Food and Drug Administration (FDA) in July 2015 and by the European Medicines Agency (EMA) in November 2015. In Switzerland, the drug was licensed in September 2016; however, reimbursement by health insurers is not yet compulsory. As this therapy offers a new opportunity in Phe508del homozygous patients with end-stage cystic fibrosis pulmonary disease, we decided to use LUM/IVA on a “compassionate use” basis. In every individual case we seek reimbursement from health insurance.

Our aim was to evaluate if this patient cohort tolerates LUM/IVA treatment. Further, we hypothesised that LUM/IVA might lead to clinical stabilisation, even in patients with end-stage cystic fibrosis pulmonary disease.

Material and methods

This was a single-centre prospective observational study in which LUM/IVA (Orkambi[®], Vertex Pharmaceuticals, MA, USA) was taken orally by Phe508del homozygous patients with end-stage cystic fibrosis pulmonary disease. The study was conducted from January 2016 to January 2017. All patients were cared for at our Adult Cystic Fibrosis and Transplant Centre at the University Hospital Zurich. At the time, we were caring for 102 patients with cystic fibrosis of whom 47 were Phe508del homozygous. Data for the 6 months before LUM/IVA initiation were collected prospectively. Basic patient information was obtained from the electronic patient files at the University Hospital Zurich. The study was approved by the local Ethics Committee (EK 2016-01494).

We included all adult patients with cystic fibrosis from our centre with Phe508del homozygous genotype and who had a FEV₁ <40% predicted, or were under evaluation or already listed for lung transplantation in accordance with international guidelines [6]. No patient refused a trial of LUM/IVA. All patients were excluded from participation in ongoing trials of CFTR modulators in Switzerland because of their FEV₁ of <40%.

Exclusion criteria were as follows: history of solid organ or haematological transplantation, pregnancy or breast-feeding, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of reference range (ULRR); or ALT or AST >3 × ULRR and bilirubin >2 × ULRR.

As there is limited information about the tolerability of LUM/IVA in cystic fibrosis patients with end-stage pulmonary disease, we decided to implement the following protocol. Patients received the first tablet in the outpatient clinic with a 3-hour monitoring period. Afterwards, the drug dose was increased stepwise until the maintenance dose was reached (two tablets twice daily: LUM 400 mg every 12 h and IVA 250 mg every 12 h). Our cystic fibrosis nurse followed patients up by phone every third day, assessing patients' overall wellbeing and the drug tolerability. If the patient tolerated LUM/IVA, the daily dose was increased by one tablet. In the case of adverse events, the dose was reduced by one tablet. In general, when there was an amelioration of symptoms due to adverse events after a dose reduction of one tablet, we increased the dose again by one tablet after a stabilisation period of 2 weeks. If ad-

verse events persisted despite dose reduction by one tablet, we further reduced the dose by one tablet. Patients were evaluated every 4 weeks in the outpatient clinic.

Outcome data comprised acute exacerbation rate according to the modified Fuchs-criteria [7]. The modality of treatment was based on clinical judgement of the treating physician (ambulatory vs home treatment). Further outcome parameters were: 6-minute walking distance (6-MWD), FEV₁, forced vital capacity (FVC), mid-expiratory flow (MEF 25–75%), sweat chloride, body mass index (BMI) and quality of life. Lung function tests were obtained accordingly [8]. Quality of life was assessed using a standard questionnaire (The revised German Cystic Fibrosis Questionnaire [CFQ-R]); from the total of 12 domains, we focused on the two most relevant (“physical” and “respiratory”) according to the patients' feedback [9]. Sweat chloride was measured between 1 week before starting with LUM/IVA and the end of the 6 months of follow-up at University Children's Hospital Zurich, a Swiss national reference centre, with use of the macroduct collection system. The number of acute exacerbations during the 6 months before treatment were recorded. Respiratory-related adverse events (dyspnoea, chest-tightness, increased sputum production, pulmonary exacerbation) were recorded as described by Popowicz et al. [10].

Detailed drug information was given to the patient by the physician. All patients agreed to participate in a CFTR modulator trial. Written informed consent was collected from all patients on the general informed consent form (“Generalkonsent”, USZ). In Switzerland, criteria for treatment success of CFTR modulator therapy exist only for IVA. Therefore, we defined treatment success in accordance with Wainwright et al. [5] as follows: reduction of the acute exacerbation rate by at least 30% or absolute improvement in FEV₁ or FVC by 3% or improvement in BMI by 1%. If patients on the transplant waiting list, fulfilled a minimum of two of the given criteria, this resulted in inactivation on the waiting list. In the case of treatment success, therapy continued.

Statistics

Descriptive statistics were used for this retrospectively collected data. Because of the small sample size and not normally distributed data, median values of the physiological variables were computed. Paired comparisons were performed by t-tests. An exact sign test was used to compare the differences in the scores of the CFQ-R domains “physical” and “respiratory”. A p-value <0.05 was considered statistically significant.

Results

At the cut-off date, 20 patients were on a trial of LUM/IVA. Here, we present 10 patients who had already completed 6 months of follow-up. Respiratory adverse event data during the first month were recorded for all 20 patients. Complete data on 6-MWD and sweat chloride were available for all but one patient, and completed CFQ-R results for all but two patients.

Baseline characteristics (n = 10) are as follows. All patients were male, all had pancreatic insufficiency, six patients had cystic fibrosis-related diabetes mellitus and seven patients had chronic *Pseudomonas aeruginosa* pulmonary in-

fection; no patient had *Burkholderia cepacia* complex. Patients were suffering from severe airway obstruction with a median FEV₁ of 1.31 L (32% predicted, 18–44%), one had a FEV₁ <20% predicted, four had a FEV₁ between 21 and 30% predicted and four had a FEV₁ between 31 and 40% predicted. For the 20 patients in the respiratory adverse event analysis, median predicted FEV₁ was 1.23 L (29.5% predicted, 16–49%), two had a FEV₁ <20% predicted, nine had a FEV₁ between 21 and 30% predicted and seven had a FEV₁ between 31 and 40% predicted. Three patients were on a waiting list for lung transplantation, and one patient was being evaluated for lung transplantation.

Most patients suffered from respiratory adverse events during treatment initiation, starting just a few hours after the first intake, and these were present in 95% after 24 hours, mainly chest tightness and increased sputum production (table 1). After 1 month, events persisted in only 35% of patients. All but three patients were at full dose by 1 month. One patient had to stop LUM/IVA indefinitely 24 hours after the first tablet intake owing to severe chest tightness. Therapy was stopped after 2 months in one patient and after 6 months in two patients because of lack of clinical success. Of these three patients, two subsequently had a successful lung transplant.

Median acute exacerbation rate decreased from 2.5 (range 0–6) before treatment to 1 (0–4) at 6 months ($p = 0.0718$). There was an increase in median FEV₁ from 32% predicted

(18–44%) to 34.5% (21–46%) ($p = 0.292$) and in median FVC from 56% predicted (21–60%) to 59% (40–71%) ($p = 0.2179$). Median MEF 25–75% remained unchanged ($p = 0.784$). An increase in 6-MWD of median 33 m was noted ($n = 9$; $p = 0.6086$). Sweat chloride decreased significantly by a median 25 mmol/l ($n = 9$; $p = 0.0003$) (fig. 1). Median BMI increased from 19 kg/m² (17–24.9) to 19.9 kg/m² (16.2–25.3) ($p = 0.1488$). The score of the CFQ-R domain “physical” elicited a statistically significant median increase at month 6 compared with baseline ($p = 0.031$), whereas the score of the “respiratory” domain did not significantly change ($n = 8$; $p = 0.22$). Outcome parameters are shown in table 2. As a result of clinical improvement, three patients are currently paused on the transplant waiting list.

Discussion

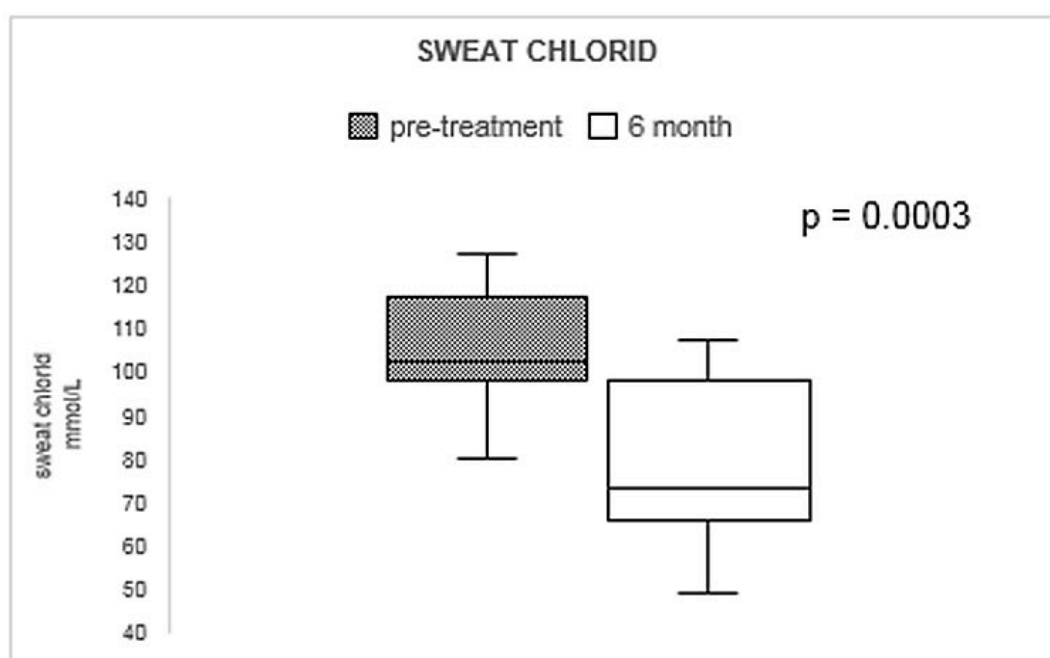
Our study showed that Phe508del homozygous patients, even with end-stage cystic fibrosis pulmonary disease, tolerated LUM/IVA, although respiratory adverse events were severe. The low dropout rate was probably due to our protocol, with a low starting dose of LUM/IVA and careful dose increases thereafter. In our patients (who were not eligible for phase III clinical trials), the clinical benefit was mainly from a reduction in acute exacerbation rate and stabilisation of lung function on treatment with LUM/IVA.

Table 1: Respiratory-related adverse events from patients ($n = 20$), at 3 hours, 24 hours and 1 month, according to Popowicz et al [10].

	3 hours	24 hours	1 month
Dyspnoea, n (%)	0	1 (5%)	1 (5%)
Chest tightness, n (%)	1 (5%)	10 (50%)	1 (5%)
Increased sputum production, n (%)	1 (5%)	8 (40%)	3 (15%)
Pulmonary exacerbation, n (%)	0	0	2 (10%)

n = number of participants.

Figure 1: Change in sweat chloride from pre-treatment to 6 months of treatment.



In the combined TRAFFIC and TRANSPORT studies, inclusion criteria were a FEV₁ at time of screening of 40–90% predicted [5]. Of 1108 patients included in the efficacy analysis, 81 had a FEV₁ that decreased to <40% predicted between baseline and screening with a mean FEV₁ of 37% predicted. A subgroup analysis of these patients showed an absolute increase in FEV₁ of 3.3 to 3.7% predicted [11]. In contrast, our patients suffered from more severe cystic fibrosis pulmonary disease, with a median FEV₁ of 32% predicted. In our cohort, median FEV₁ increased by 2.5% and FVC by 3% predicted on LUM/IVA. Although this change was not statistically significant and the sample size was small, it is an important finding that lung function at least stabilised in this patient cohort.

Besides the increase in change of 6-MWD (median 33 m), weight gain in this underweight cystic fibrosis population with end-stage pulmonary disease was another remarkable finding. In our view, the most important clinical benefit was the reduction in acute exacerbation rate, mainly leading to clinical stabilisation or even improvement. The health-related quality of life domain “physical” significantly increased, confirming our clinical observation that most patients on LUM/IVA have improved wellbeing and mobility. On the basis of the defined treatment success criteria, three patients listed for lung transplantation were paused on the waiting list.

At 6 months’ follow-up, sweat chloride decreased, demonstrating an effect on chloride channel function. Interestingly, the decrease in change of sweat chloride did not correlate with an improvement in other biomarkers investigated in our patients. Boyle et al. showed that there was no corresponding improvement in FEV₁ and sweat chloride in Phe508del homozygous patients with cystic fibrosis treated with LUM/IVA. The authors concluded that there is a differential effect on CFTR function in the lung and sweat glands [12]. Recently published combined analysis of data from eight clinical trials evaluating the effect of IVA on sweat chloride showed that sweat chloride level changes appear to be a predictive pharmacodynamic biomarker of lung function changes on a population basis, but are unsuitable for the prediction of treatment benefits for individuals [13]. However, because of the small sample size, our results are underpowered to answer this question and, of course, the between-test variability must be considered [14].

Our patients suffered from intense and early respiratory-related adverse events. The subgroup analysis of the TRAFFIC and TRANSPORT studies also showed that the incidence of respiratory adverse events was greater in the LUM/IVA group than in the placebo group. Such events

occurred earlier in the patients with FEV₁ <40% predicted [11]. The same has been shown in the real-world studies evaluating the effect of LUM/IVA therapy in Phe508del homozygous cystic fibrosis patients with end-stage pulmonary disease from Popowitz et al. and Hubert et al., in which all but one patient were on full-dose therapy [10, 15]. In the most recent prospective US multicentre study by Taylor-Cousar et al., the overall incidence of respiratory adverse events in the 24 weeks of the study was 65%, with an early onset; 39% of the patients initially received half of the recommended dose for 1 to 2 weeks, followed by dose escalation [16]. In our patient cohort, the incidence of respiratory adverse events was 95% after 24 hours, but down to 35% at 1 month. However, caution is needed when comparing these different studies because of heterogeneity in the assessment and reporting of respiratory adverse events. Clinicians should be aware of this and be in close contact with patients during treatment initiation. If respiratory symptoms increased after stepwise dose augmentation, patients were advised to reduce their dose. We observed that administration of short-acting and/or long-acting bronchodilators ameliorated chest tightness. This effect has also been shown in a study with healthy subjects [17]. Recent studies had dropout rates of 30% (24% due to adverse respiratory events, n = 53) starting with the full (recommended) dose, 32% (n = 19) and 25% (n = 12), respectively [10, 15, 18]. In the study reported by Taylor-Cousar et al. (in which 39% of patients started with half of the recommended dose), there was a dropout rate of 17% (n = 46) due to any adverse events, but 24% of patients did not complete the 24 weeks of treatment. Taking all patients from our cohort (n = 20), including 10 patients with a complete 6 months of follow-up, we had a dropout rate of 20%, mainly due to lack of clinical success; only one patient stopped treatment because respiratory adverse events. We believe that our stepwise approach helped to ameliorate and/or improve tolerance of these adverse events. However, patients such as ours should be carefully selected before treatment initiation, as they often have little reserve. We propose that these patients should be started on LUM/IVA treatment only in experienced cystic fibrosis centres.

Our study had limitations. It was a single-centre, investigator-driven study with a small sample size and no matched controls. By chance, the 6-month follow-up only included males, one female was included in the adverse event analysis of the total cohort. This has to be considered, as a gender difference exists among cystic fibrosis patients, and females might potentially suffer from more severe adverse events. We had no change of concomitant medication during the study. Adherence to treatment is difficult to assess.

Table 2: Outcome parameters at baseline and after 6 months.

	Baseline	6 months	p-value
AER (n = 10)	2.5 (0–5)	1 (0–4)	0.072
FEV ₁ (% predicted) (n = 10)	32 (18–44)	34.5 (21–46)	0.292
FVC (% predicted) (n = 10)	55 (21–50)	59 (40–71)	0.218
Sweat chloride (mmo1/1) (n = 9)	102	73	0.0103
BMI (kg/m ²) (n = 10)	19 (17–24.9)	19.9 (16.2–25.3)	0.149
CFQ-R score (n = 8)			
Domain “physical”	59 (37–100)	90 (63–100)	0.031
Domain “respiratory”	53 (33–100)	75 (50–100)	0.220

n = number of participants AER = acute exacerbation rate; BMI = body mass index; CFQ-R = the revised German Cystic Fibrosis Questionnaire; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second

However, we found no clear evidence of poor adherence. Regarding the high cost of the CFTR-modulator therapy, we were unfortunately unable to compare the cost of lung transplantation and post-transplant care vs LUM/IVA treatment.

Lung transplantation is the ultimate treatment option for end-stage cystic fibrosis pulmonary disease despite maximal therapy [6]. New treatments including CFTR-modulators, ought to be tested [19]. If lung transplant candidates stabilise clinically, conditions for transplantation, when finally required, improve. This is particularly important in countries such as Switzerland with a low organ donation rate and long waiting times for suitable donor organs.

To conclude, our results show that in Phe508del homozygous cystic fibrosis patients with end-stage lung disease, LUM/IVA is tolerated although respiratory adverse events are severe and occur early. We propose that all suitable cystic fibrosis patients with end-stage pulmonary disease receive LUM/IVA treatment, under a protocol with stepwise increases of the dose.

Disclosure statement

CM and TK received national advisory board fees from Vertex Pharmaceuticals. LCH received speaker and advisory board fees from Vertex Pharmaceuticals. CB received national and international advisory board fees and speaker fees from Vertex Pharmaceuticals.

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