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Bridging for lung transplantation with lumacaftor/ivacaftor

Case report

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Introduction

Cystic fibrosis (CF) is a multi-organ disease caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene, with consequent dysfunction of the CFTR channel. The most common mutation in CF is delta F508. CFTR-modulating therapy with lumacaftor/ivacaftor corrects (lumacaftor) the misfolded CFTR channel and potentiates (ivacaftor) its function at the cell surface [1].

Task 1
What is the impact of a malfunctioning CFTR channel in the lungs?

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The case of a young female cystic fibrosis patient, homozygous for delta F508 and with terminal respiratory insufficiency, who started treatment with lumacaftor/ivacaftor
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Answer 1
Lack of chloride transport through the CFTR channel causes a thick and motionless layer of mucus in the lungs. This impairs the removal of bacteria, fungi and viruses leading to chronic lung infections and inflammation [2].

Several studies have investigated the effects and side-effects of these new treatments [3]. In these studies, primary and secondary end-points have been changes in forced expiratory volume in 1 s (FEV_1) % predicted, incidence of pulmonary exacerbation, changes in body mass index (BMI) and respiratory symptoms. Lumacaftor/ivacaftor has resulted in a significant, although limited increase in FEV_1 % predicted in patients homozygous for the delta F508 mutation with variable results regarding the effects on BMI [4].

In this case report, we demonstrate the impact of lumacaftor/ivacaftor on routine inflammatory markers and on the general condition in a CF patient with end-stage lung disease waiting for a lung transplant.

Case history

A 21-year-old female with CF, homozygous for the delta F508 mutation and pancreas insufficient, had been diagnosed with CF at the age of 15 months due to failure to thrive. The patient had chronic lung infection with *Staphylococcus aureus*, *Stenotrophomonas maltophilia* and *Aspergillus fumigatus*. She did not have CF-related diabetes or CF-related liver disease. After considerable pulmonary instability and declining lung function she was accepted onto the lung transplant waiting list in October 2013.

Task 2
When should patients with CF be considered for lung transplantation?

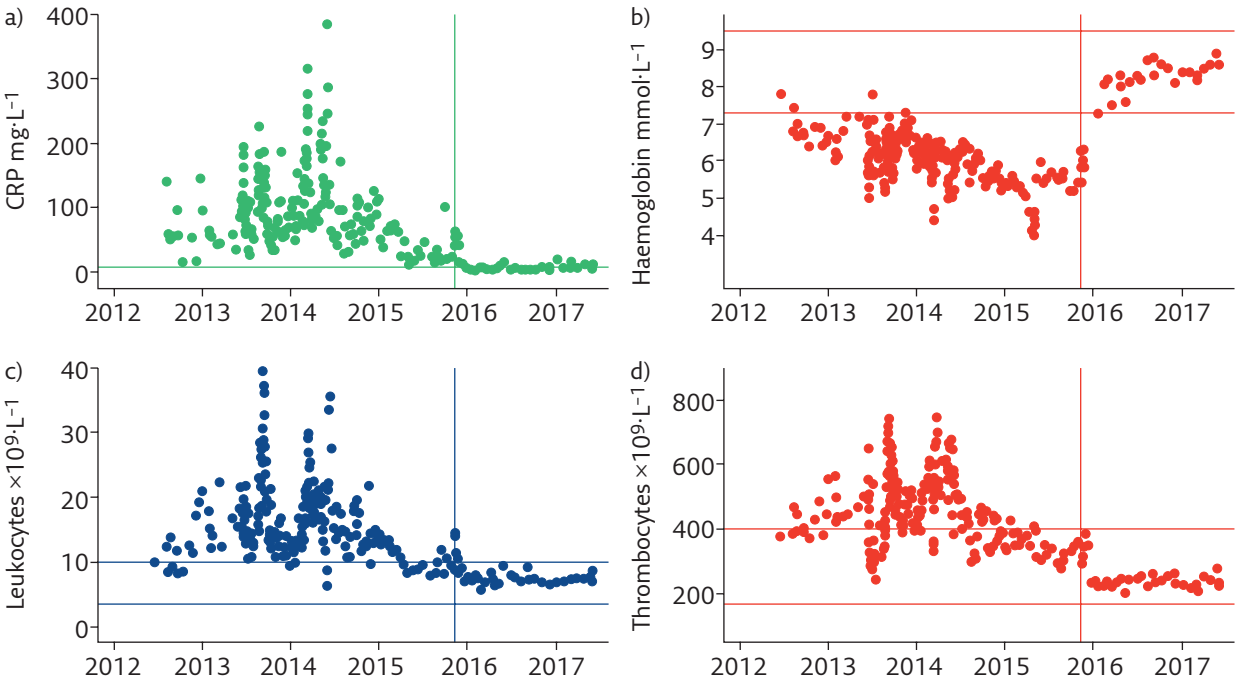

Figure 1 *Scatter plots of a) CRP, b) haemoglobin, c) leukocytes and d) thrombocytes over time. Horizontal lines represent the reference ranges for each parameter. Vertical lines indicate the onset of treatment with lumacaftor/ivacaftor. Labels on the x-axis indicate the start of each year.*

Answer 2

- FEV1 of ≤30% predicted or a rapid decline in younger patients.
- Oxygen therapy for hypoxaemia.
- Frequent pulmonary exacerbations that respond poorly to treatment [5].

In November 2015 she began treatment with lumacaftor/ivacaftor. Prior to initiation of treatment with lumacaftor/ivacaftor FEV1 was 0.59 L (20% predicted) and BMI was 16.9 kg·m^{-2}.

For comparison we analysed the mean values of haemoglobin, platelet count and inflammatory markers (C-reactive protein (CRP) and leukocyte counts) 5 years prior to lung transplantation. We also investigated the effect of lumacaftor/ivacaftor on the 6-min walk test (6MWT). This test was performed once every 3 months in the department of respiratory medicine, while the patient was on the waiting list for a lung transplant. Data analysis was performed using STATA 13 (StataCorp LP, College Station, TX, USA; 2013). All end-points were categorised into two groups: before and during treatment with lumacaftor/ivacaftor.

All four parameters changed significantly (figure 1). The inflammation parameter CRP decreased significantly after starting lumacaftor/ivacaftor from a mean of 99.08 mg·L^{-1} (95% CI: 91.31–106.86) to 8.24 mg·L^{-1} (95% CI: 7.56–23.89) ($p<0.001$) and leukocyte counts decreased significantly from a mean of 16.49×10^9·L^{-1} (95% CI: 15.72–17.28) to 8.24×10^9·L^{-1} (95% CI: 7.45–9.03) ($p<0.001$). Figure 1a and c illustrates a stabilisation towards the point of initiation of lumacaftor/ivacaftor treatment. In addition, both parameters had a transitory increase after the onset of treatment.

Task 3
Should chronic lung inflammation be treated with corticosteroids?

Answer 3
Corticosteroids have no effect in patients with CF. Chronic maintenance therapy consists of:

- Mucolytics, which degrade mucus, improve lung function and reduce the frequency of pulmonary exacerbation;
- Hydrator therapy, which hydrates airway surfaces improving lung function and reducing the frequency of pulmonary exacerbation; and
- Antibiotic therapy, for the eradication or suppression of bacterial infections [5].

Haemoglobin increased significantly from a mean of 6.01 mmol·L^{-1} (95% CI: 5.93–6.09) to 7.74 mmol·L^{-1} (95% CI: 7.34–8.13) (p<0.001). Figure 1b illustrates the increase in haemoglobin after a steady drop in the time prior to treatment. High levels of thrombocytes from reactive thrombocytosis decreased significantly from a mean of 466.3×10^{9}·L^{-1} (95% CI: 452.2–480.6) to 261.3×10^{9}·L^{-1} (95% CI: 243.7–278.9). The patient did not receive blood transfusions during the course of treatment.

Following treatment, FEV1 at week 26 was 0.55 L (18% predicted) and BMI was 17.4 kg·m^{-2}. At week 55, FEV1 was 0.65 L (21% predicted) and BMI was 17.6 kg·m^{-2}.

The patient experienced considerable changes in her general condition after starting lumacaftor/ivacaftor treatment. The patient's need for oxygen therapy stopped and, from being mostly immobilised using wheelchair, she regained walking ability, improving her 6MWT from a mean of 246.4 m (95% CI: 198.5–294.4) to a mean of 374.6 m (95% CI: 307.5–441.7) (p=0.002). She had social interaction with friends, which had not taken place for several years.

In June 2017, after 3.5 years on the waiting list, the patient had a lung transplant.

Discussion

We report the case of a young female CF patient homozygous for delta F508 and with terminal respiratory insufficiency, who started treatment with lumacaftor/ivacaftor and experienced a significant reduction in inflammatory markers and a significant increase in haemoglobin. These changes led to a significant improvement of physical ability and of quality of life; however, the patient did not experience an increase in FEV1 after starting therapy due to irreversible lung damage. Ultimately, treatment with lumacaftor/ivacaftor was essential in bridging to lung transplantation. Early effects of lumacaftor/ivacaftor have been demonstrated with respiratory events [6]. Our data on leukocytes and CRP support these findings. Our findings from blood samples indicate new positive outcomes, which should be investigated in larger studies.

Conflict of interest

None declared.

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